Interim Session, Rochester, Minnesota, November 29-30, 1958
Semi-Annual Meeting, Board of Regents, Minneapolis, Minnesota, December 1, 1958

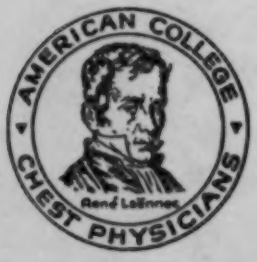
VOLUME XXXIV NUMBER 3

DISEASES

of the

CHEST

OFFICIAL PUBLICATION



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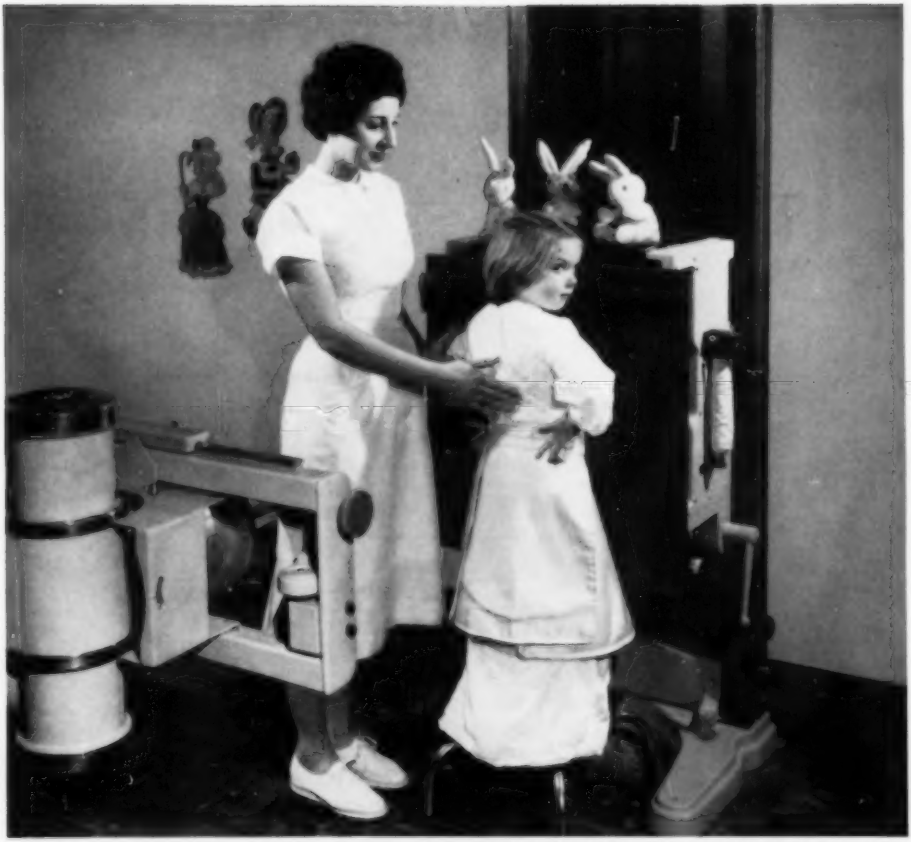

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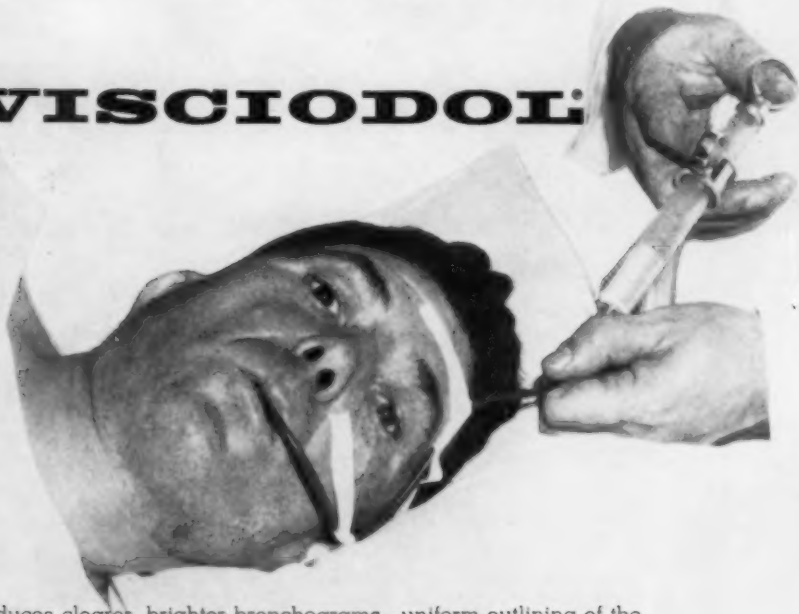

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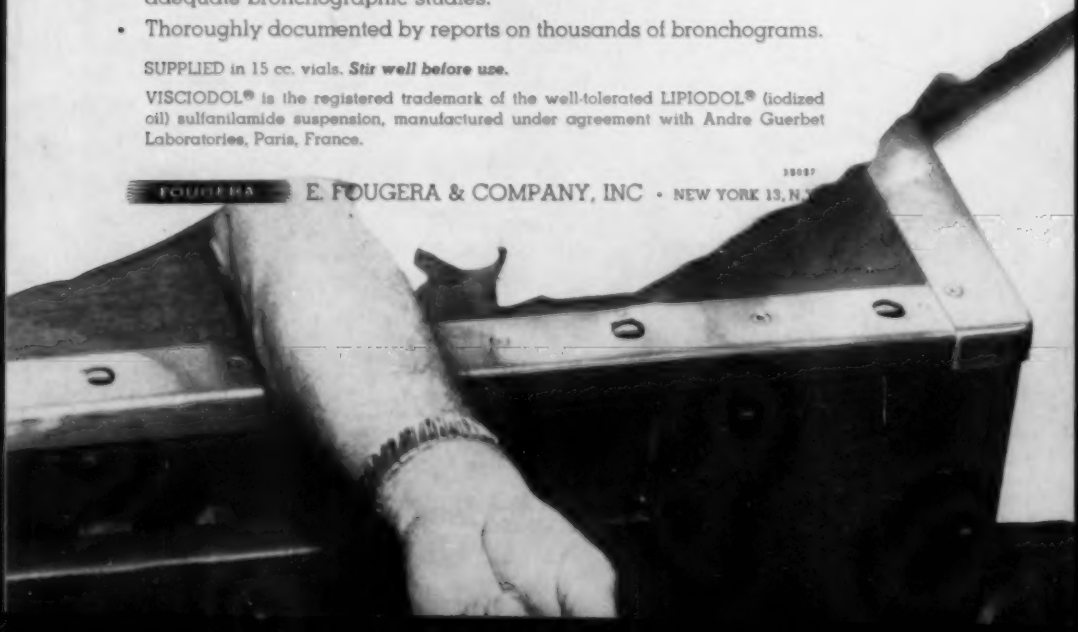

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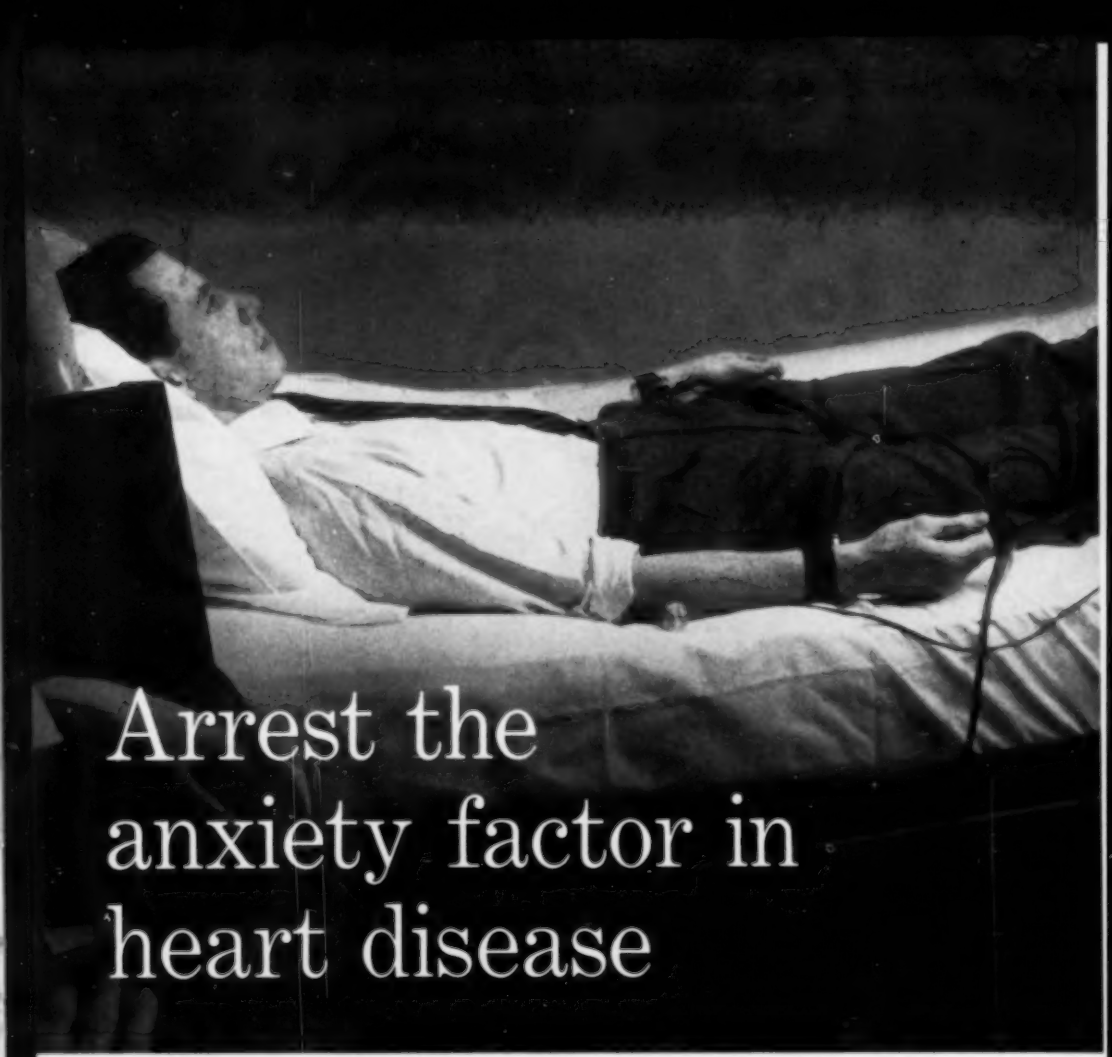

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*Miller, J.B., et al.: Ann. Allergy, 12:611, Sept.-Oct., 1954.

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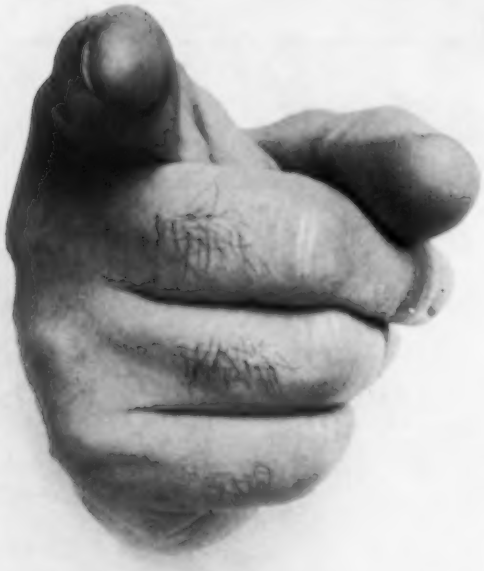

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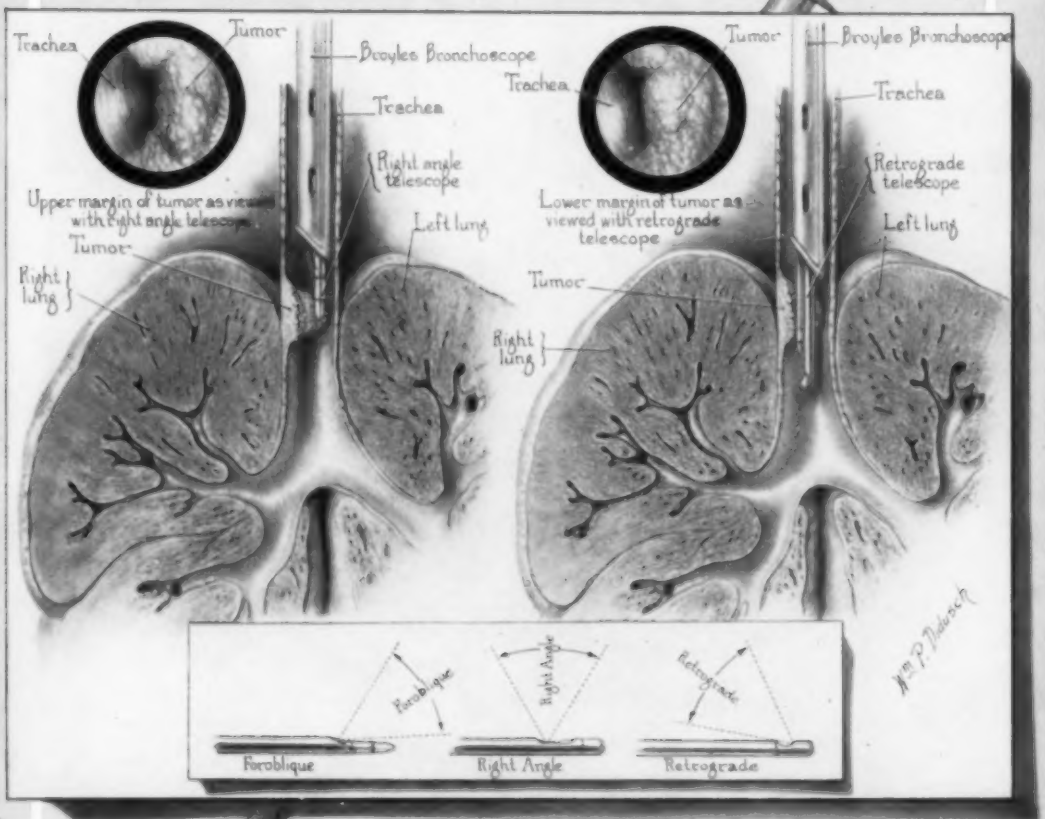

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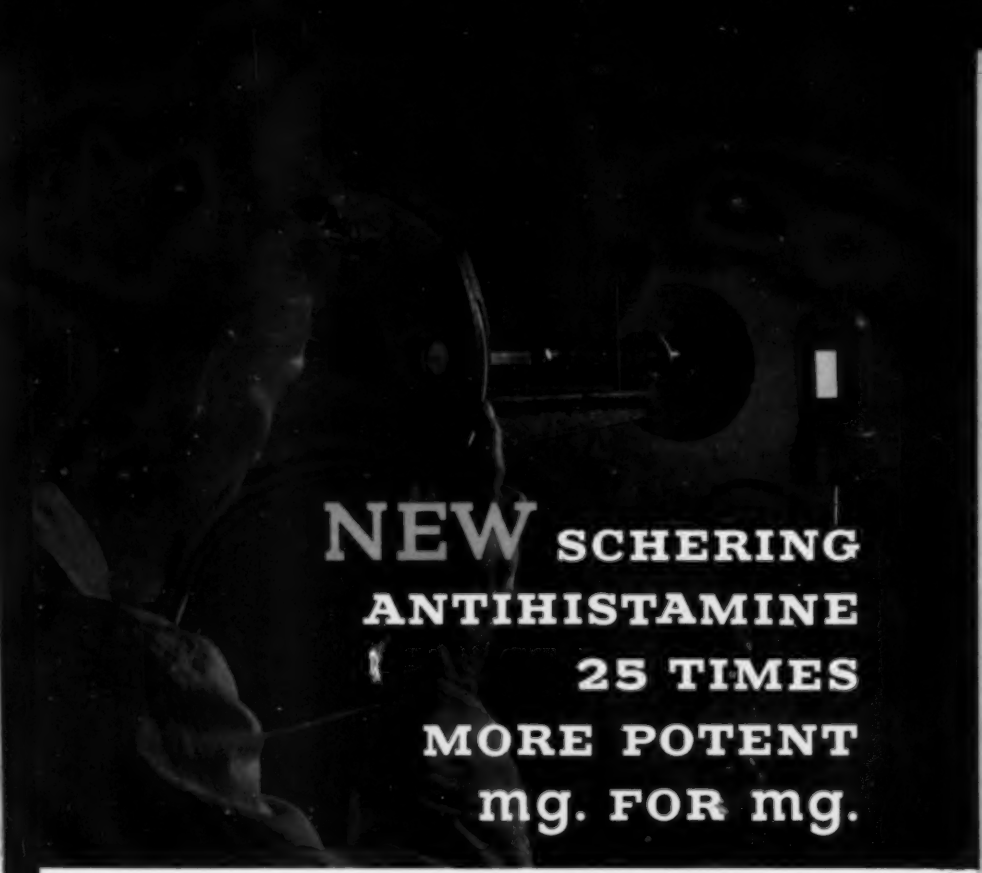

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1. *Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Card.* **1**:891, *March 1958.*
2. *Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology* **8**:504, *Dec. 1957.*

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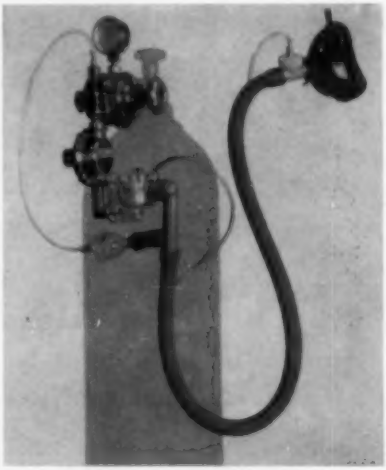

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Toxicity, sensitization or complete intolerance	*1. More prolonged hospital stay.* *2. Overall cost of special care by physician, nurse and pharmacist—desensitization, dosage adjustment, etc.*
Patient resistance to PAS form and dosage regimen	*1. Cost of medication thrown away by the patient.* *2. More prolonged hospitalization resulting from inadequate dosage.*

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1. Molthan, L., Cohen, R.V., and Zarafonetis, C.J.D.: Am. Rev. Tuber. 71:220, 1955.
2. Cohen, R.V., Molthan, L., and Zarafonetis, C.J.D.: Dis. Chest 30:418, 1956.

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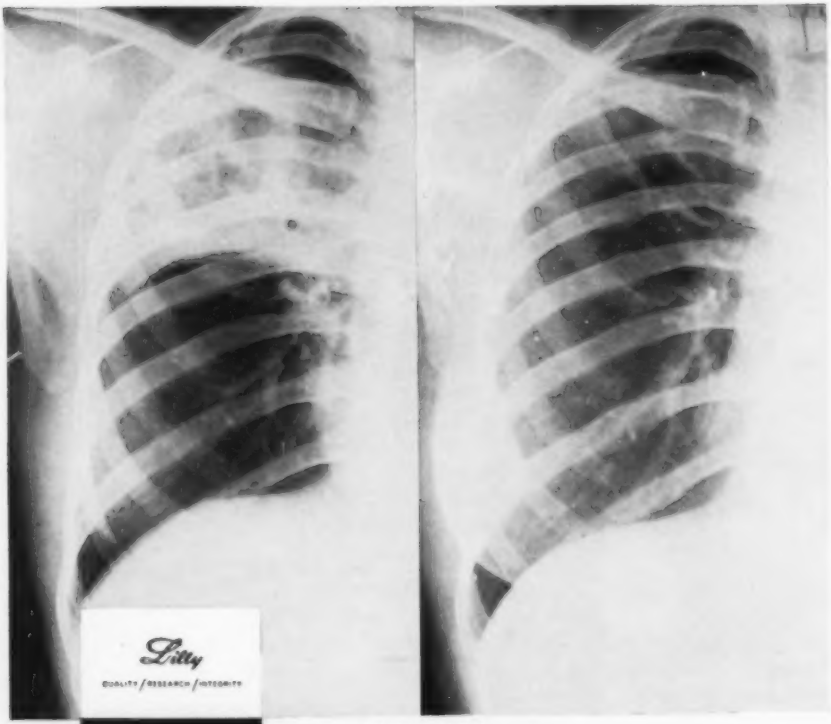

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DISEASES of the CHEST

VOLUME XXXIV SEPTEMBER, 1958 NUMBER 3

Speculations on the Future Treatment and Control of Tuberculosis*

H. CORWIN HINSHAW, M.D., F.C.C.P.**

San Francisco, California

Speculations about the future appeal to us all. Someone has said that he was mostly interested in the future because he expected to spend the rest of his life there.

Trends have become established in the fields of tuberculosis control and treatment which, if they continue in their present direction, may well affect the practice of medicine in a radical manner. Is it possible that home treatment will supplant sanatorium treatment? Or, on the other hand, will the present trend to socialization of tuberculosis medicine continue, with less and less of private practice? Is the time near when the 100,000 beds now occupied by patients with tuberculosis can be used for other purposes? Can the taxpayers be relieved of the enormous cost of the Veterans Administration Tuberculosis program? Is it possible that the present Veterans monetary benefits for disability from tuberculosis can be abolished; assuming that no true disability exists following successful modern treatment?

Most importantly, are we as physicians doing all that we could do to direct the stream of events in this changing field? If we can agree on what is right and what is best for our patients and the public we should bend all efforts to see any necessary reforms enacted to bring about what is best.

Most of us serve as doctors—physicians is a better word—and we serve individuals, rather than the mass of men. While we are interested in local and national statistics, it is in a rather detached way, for what we do as individuals carries little weight in the broad sense. We serve as *personal* physicians—I like that word, use it often—we are *personal* physicians to rather small numbers of people. We are responsible for their health and welfare, but we share their other problems; their triumphs as well as their problems. We seek, above all, to protect them from the dangers of disease; especially the unseen health hazards from which they cannot protect themselves. Let us promote the idea that each man, woman and child should choose a personal physician and refer to him all health problems.

*Presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957.

**Clinical Professor of Medicine, Stanford University School of Medicine.

The personal physician, not the public health clinic, is the one to whom the patient of the future may look for protection against perils of thoracic disease. I mention thoracic disease, not alone because I am talking to this group, but because such conditions as degenerative heart disease, bronchogenic carcinoma and even tuberculosis are profoundly important to those who have chosen you as their personal physician. Perhaps these diseases are preventable—you might want to argue that point—but they are detectable, especially the pulmonary diseases, by the rather simple means of chest x-ray. I have included tuberculosis in the list because its curability is nearly 100 per cent in those persons who have annual chest x-ray films and are well advised about the findings. I should stress bronchogenic carcinoma because of its mounting prevalence and the urgent need for its recognition *before* it produces symptoms. Of the visceral cancers it is one of the most curable when treated during the earliest stage at which it can be detected—few cancers of man can be detected so early, by the personal physician.

Minifilms vs Megafilms:

Case finding, another word for diagnosis, is the obvious "sine qua non" in all tuberculosis endeavour, whether private practice or public health. The minifilm mass survey technique has now undergone thorough trial and demonstration. It has served as a great educational method, for doctors as well as the public. It is my opinion that the future use of this technique is predictable. It will not be used for periodic mass surveys of the general public in the United States, the task is too great and the yield is now too small for the true cost of such undertakings. On the other hand, special population groups should be surveyed by this or another method. I refer to groups with a high incidence of tuberculosis; food handlers, prisoners and inmates of charity hospitals and domiciliary institutions. School teachers, "baby sitters" and others who associate closely with children constitute a special group.

There is no virtue in minifilms, as such. Even the factor of economy has been exaggerated greatly. Economy is partly the result of hasty diagnosis by "cheap help" or donated services. It should take more time, not less time, and more skill, to study a minifilm accurately and since time is a most expensive ingredient in total true cost the conventional 14 × 17 film may be the cheapest. Cost of equipment and its depreciation may exceed the cost of film when the number of patients is small.

We cannot pass the subject of minifilms without mention of radiation exposure. There has been much speculation and no little hysteria about exposure hazards in radiology. Chest x-ray films are less hazardous than many radiologic examinations because (1) little radiation is necessary for penetration of the air-containing thorax (unlike the abdomen), (2) there need be no direct radiation of the reproductive organs and scatter radiation is extremely slight (a luminous dial wrist watch provides as much radiation in one week as a chest x-ray film). Nevertheless we must call your attention to the fact that one minifilm involves as much radiation exposure as 10 to 25 14 × 17″ films. Whenever the factor of exposure

is considered—as in children—preference should be for the 14 × 17″ chest film. One complete "G.I. series" may involve as much gonadal exposure as scores or hundreds of chest x-ray films.

If the fears of the alarmists should be substantiated, radiologic examinations of the future may be done by means of amplified images, a technique resembling television which could reduce radiation to a negligible amount. There is not the slightest reason to fear the annual or semi-annual conventional chest x-ray film, in my opinion. If minifilms are to be used it might be desirable to use only the new mirror cameras with such great light gathering capacity as to reduce exposure and scatter considerably. Each of us should determine if our patients are receiving needless radiation because of failure to provide limiting cones or similar screens for the gonads.

State Medicine vs Private Medicine:

It has become tradition in many communities that tuberculosis problems will be cared for by public agencies. This is based upon the supposition that private care is too expensive or not good enough and the fact that this is a contagious disease. The time may be approaching when these suppositions can be questioned and these facts modified.

Speaking of quality of medical care, I doubt if any community now lacks private physicians who are thoroughly trained in the management of pulmonary diseases. Good radiologic and laboratory services are available universally throughout this country. These conditions did not exist 20-30 years ago when many of the present regulations were devised.

The cost of treating tuberculosis has diminished and may be even further reduced. Prolonged and stringent bed rest is no longer necessary. Often an "attack" of tuberculosis involves less expense and less disability than a heart attack and certainly tuberculosis is much the less common of the two.

I have a concrete proposal for the insurance companies and welfare funds which now exclude tuberculosis coverage. When writing a policy for sickness expense insurance (don't say health insurance) offer to cover tuberculosis treatment for anyone who will submit a negative chest x-ray film and who has annual films thereafter. I don't believe that the claims will be appreciable.

Tuberculosis is a contagious disease. It is essential that those who might disseminate the infection be treated until they are safe associates. The public must supply this service if it is not provided for otherwise, not only for tuberculosis but also for the many other dangerous contagious diseases. Formerly tuberculosis was communicable for a long period, but this situation has changed. A great majority of patients, certainly more than 90 per cent of those who accept modern therapy and even a greater percentage of those who have had annual negative chest x-ray films, will cease to disseminate tubercle bacilli within several weeks after treatment is started. The time is approaching—perhaps it is here—when tuberculosis need not be considered as a problem of state medicine, without

regard to the economic status of the patient, because of its public health aspects.

If patients are to pay for care of tuberculosis through prepaid insurance—and I firmly believe that they should and can do so—our public hospitals should be able to recover costs of treating such patients. Often this is now the case but in the future this source of revenue may largely supplant the contributions of the taxpayer; a welcome change for taxpayers and politicians alike.

In this day of reduced tuberculosis bed occupancy it is interesting to see the development of a real sense of competition for the patient. For example, the veteran may choose between the county hospital, a private hospital (through insurance benefits) or a Veterans Administration Hospital. Each of these is bidding for his patronage and attempting to deserve it by improvements in service. Here, as never before, the spirit of competition may serve a noble purpose.

Speaking of costs; the cost of a good individual sickness expense insurance policy which covers nearly all diseases is about the same as the cost of one package of cigarettes daily. The cost may be less than this for the more sensible deductible types of policies. Anyone who can afford to smoke can afford to buy such insurance. Tell that to your patients—but frequently. Another comparison; the annual cost of all inclusive medical care throughout a lifetime is less than the cost of keeping an automobile in repair. An ordinary illness costs less than a minor automobile repair bill or a smashed fender from a minor accident. A serious illness costs less than trading in the serviceable old car on a new model.

Dare we predict that patients can be taught the relative values and relative costs of such things as medical care and automobile care? If not is it reasonable to propose that the government should buy us new tires and clean our spark plugs rather than supply us with some health services which we may consider less important? These problems of medical economics should be the task of doctors, not politicians.

Treatment of Recently Converted Tuberculin Reactors vs Vaccination:

This is logical and may well become standard practice. My appeal will be for some truly adequate study to determine the needs and techniques for therapy. If a simple treatment, such as isoniazid alone, is adequate the procedure will become very popular. I, among many of you, have serious doubt about the adequacy of isoniazid alone. Simply because we are treating an invisible infection and a symptomless one does not necessarily imply that it will be overcome more readily. Actually we are treating this patient for all time to come. We are aiming at eradicative therapy, if at all possible, and this is truly a big task for isoniazid alone.

Much of our reasoning in tuberculosis problems has been on a mass population basis. I expect to see more personal consideration of such problems in the future. The pediatricians are doing it now. Many children receive annual tuberculin tests and some who convert will be treated. As soon as these people cease to be children the risk does not cease, yet it is forgotten. I believe that the personal physician of the immediate

future will carry out an annual birthday health appraisal examination, including a tuberculin test. Prophylactic treatment at the time of conversion is a logical substitute for BCG vaccination and on the whole more practical in the U.S.A.

If non-living antigenic material is ever extracted from the tubercle bacillus such preventive treatment may become popular in this nation.

There is no longer any question about the relative efficacy of vaccination in tuberculosis. There also is no longer any doubt in the minds of many but that immunization is far from the answer to the problems of tb control.

BCG is indicated in those areas of the world where a majority of persons become sensitized to tuberculin spontaneously. This simple formula seems to be a reasonable reply to the ever recurrent question of where to recommend mass immunization. There is still hope that some non-living immunizing agent may be developed. Lacking this we should direct our attention to the vole bacillus or similar vaccine which does not consist of tubercle bacilli, not so much because it is better or safer but just to quiet any unanswerable arguments against the inoculation of tubercle bacilli into defenseless babies by big brutes of men.

According to newspaper reports mass vaccination on a compulsory basis was instituted in the Soviet Union in 1937, yet the death rate from tuberculosis nearly 20 years later is said to be about 40 per 100,000. One week from today I expect to arrive in Moscow to attend the Sixth All-Union Congress on Tuberculosis and am anticipating this opportunity of learning at first hand the opinions of those physicians who have observed compulsory vaccination during these 20 years.

The Tuberculosis Associations and the Medical Profession:

These have been the most successful and the most effective organizations of their kind in history. I am certain that we are infinitely more advanced in the program for the eradication of tuberculosis because of the National Tuberculosis Association and its affiliate local and state organizations. I believe that the medical profession should support and guide these groups which are primarily Health Educational and Propaganda groups. They need and they want medical guidance and although they have good medical guidance at the national level there is much need for greater participation by doctors at the community level. Any decline in the effectiveness of the tuberculosis association would be a real blow to every man in this room. Your effectiveness as a doctor in the field of chest diseases would diminish.

The Veterans Administration:

We have witnessed the development of a great medical organization in a little more than 10 years, an organization within an organization—the Tuberculosis Service of the Department of Medicine and Surgery of the Veterans Administration. This organization has had much to do with improving the way you and I practice medicine. Right now it is facing some new problems related to the diminished needs for its services to

patients, simply because it has done its task so well. I would be glad to give the Veterans Administration some unsolicited advice here. Fewer patients means fewer doctors, so here is a chance to improve the quality of your staff by reducing its quantity. Don't cut pay or reduce opportunities as you contract, reward your best men as you release the others. There will always be a *good* job for the *devoted* doctor in the Veterans Administration. By all means continue your educational and research activities to draw and hold the scholarly type of doctor. By all means retain and strengthen your relationships with the medical schools—the mutual advantages of this relationship cannot be overestimated. So, I predict, a smaller, more select, and no less effective elite corps of Veterans Administration physicians who will continue as leaders in this field, academically as well as in clinical practice.

I predict that expense to taxpayers can be reduced further by a realistic review of the disability benefits paid to veterans who have had tuberculosis. Those who were disabled by service connected tuberculosis deserve more generous compensation. Those who were not disabled deserve *none*. Modern treatment frequently restores the patient with tuberculosis to full productive capacity.

Tuberculosis and the Armed Forces:

Tuberculin testing, now well established by the Navy, is ideally suited to the needs of the armed forces as a tool for detection of tuberculous infection. This is particularly important because 90-95 per cent of recruits enter service with negative skin tests. Their duties carry them occasionally to parts of the world where opportunity for infection is great. Such infections should be service connected, even if only identified by a conversion of the tuberculin test. Possibly they should be treated at this stage—perhaps the armed forces could determine for us, by means of a well designed study, if they need to be treated.

Conclusions

You and I are interested in the future—we expect to spend the rest of our lives there. We expect to see more of preventive medicine in private practice. We expect to see more patients coming for annual birthday examinations which will include a chest x-ray film. We expect that when tuberculosis is found the cost of care will be borne by sickness cost insurance which the patient has been paying for on a voluntary basis. While care of the active disease may be in a hospital under the care of specialists, the patient will soon return to his home and his job and the care of his "personal physician." The annual examination of adults will include a tuberculin test, just as is now practiced by pediatricians. Conversion to a positive test may or may not require treatment but it will alert the physician to the significance of any newly developed pulmonary disease. Such management in the Armed Forces, as well as among civilians, will lead to new concepts of service connected tuberculosis. Our present laws and regulations regarding compensation are due for drastic and realistic

revisions. Already tuberculosis is losing its reputation as a killer and crippler in war and peace.

The future is destined to be a pleasant place for spending the remainder of our lives—just as the past has been.

SUMMARY

The personal physician should expect to serve ever more important functions in preventive medicine and public health.

Minifilm surveys of the future are likely to be limited to special population groups who face unusual hazards of thoracic disease.

Insurance against expenses of illness should cover such catastrophes as pulmonary tuberculosis. Present day methods of treatment have reduced the cost of treatment and the prevalence of the disease has diminished sufficiently so that such insurance need not be expensive.

Diminished bed occupancy of tuberculosis hospitals should permit the abandonment of less effective institutions and improvement of the surviving hospitals.

The treatment of recently converted tuberculin reactors appears to be a logical and feasible substitute for BCG vaccination in many social groups in the U.S.A.

Physicians in private practice should provide more direct personal support and encouragement to local and state tuberculosis associations.

The Veterans Administration and the Armed Forces will continue to provide leadership in the field of tuberculosis and related problems.

RESUMEN

Es de que el médico personal esperarse tenga siempre más importantes funciones en la medicina preventiva y en la salubridad pública.

Las investigaciones por roentgenfotografía en el futuro, es posible que se limiten a grupos especiales de población que se enfrenten a peligros extraordinarios en relación a las afecciones torácicas.

Los seguros contra gastos de enfermedad deben cubrir la tuberculosis pulmonar. Los métodos actuales de tratamiento han reducido el costo del tratamiento y la prevalencia de la enfermedad ha disminuido suficientemente de manera que el seguro no debe ser costoso.

La disminución del número de camas ocupadas debe permitir el abandonar las instituciones menos efectivas y mejorar los hospitales que resten.

El tratamiento de los reactores que han virado recientemente parece ser un substituto lógico del BCG en muchos grupos sociales de los Estados Unidos.

Los médicos en la práctica privada deben dar mayor apoyo directo y personal a las asociaciones antituberculosas locales.

La Administración de Veteranos y las Fuerzas Armadas continuarán proporcionando siendo guías en tuberculosis y en los problemas que con ella se relacionan.

RESUME

On devrait s'attendre à ce que les fonctions du médecin personnel soient de plus en plus importantes en médecine préventive et dans le domaine de la santé publique.

Les examens radiophotographiques de l'avenir pourront se limiter à des groupes spéciaux de la population exposés de façon inhabituelle aux risques des affections thoraciques.

L'assurance-maladie devrait couvrir les catastrophes telles que la tuberculose pulmonaire. Les méthodes actuelles de traitement ont réduit les frais de traitement et la fréquence de la maladie a diminué suffisamment. L'assurance pourrait en conséquence ne pas être d'un prix élevé.

La diminution de l'occupation des lits dans les hôpitaux pour tuberculeux devrait permettre d'abandonner les établissements moins actifs et d'améliorer les autres.

La traitement des individus ayant récemment viré leurs réactions tuberculiniques semble devoir remplacer la vaccination par le B.C.G. Le procédé parait logique et réalisable dans beaucoup de groupes sociaux aux Etats-Unis.

Les médecins de clientèle privée devraient apporter une aide plus directe et un encouragement aux associations tubrculeuses locales et départementales.

L'Administration des Vétérans et des Forces Armées continuera à prendre la tête de la lutte contre la tuberculose et des problèmes qui lui sont liés.

ZUSAMMENFASSUNG

Vom einzelnen Arzt muss man erwarten, dass er immer wichtigere Aufgaben in der präventiven Medizin und dem öffentlichen Gesundheitswesen dient.

Kleinbild-Röntgenaktionen sind in Zukunft wahrscheinlich begrenzt auf spezielle Bevölkerungsgruppen, die ungewöhnlichen Wagnissen hinsichtlich thorakaler Erkrankungen gegenüberstehen.

Eine Versicherung für die Unkosten bei Erkrankung sollte gegen solche Schnicksalsschläge wie Lungentuberkulose schützen. Die Methoden der Behandlung von heute haben zu einer Verringerung der Kosten der Behandlung geführt und die Krankheitshäufigkeit ist soweit zurückgegangen, dass eine solche Versicherung nicht kostspielig zu sein braucht.

Verminderte Bettenbelegung in Tuberkulose-Anstalten muss es ermöglichen, wenig rentable Einrichtungen aufzugeben und die übrigen Anstalten zu verbessern.

Die Behandlung von Fällen mit frisch positiv gewordener Tuberkulinreaktion scheint ein logischer und möglicher Ersatz für die BCG-Impfung in vielen sozialen Gruppen in den USA zu sein. Die Ärzte in der freien Praxis sollten den örtlichen und staatlichen Tuberkulose—Vereinigungen eine mehr direkte und persönliche Unterstützung und Anregung gewähren.

Die Versehrtenverwaltung und die bewaffneten Streitkräfte werden darin fortfahren, für die Leitung auf dem Gebiete der Tuberculose sowie mit ihr verwandter Gebiete zu sorgen.

Emphysema and the Lungs of the Aged: A Clinical Study*

Preliminary Report

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Pulmonary emphysema has long remained an enigmatic disease. Regarding its origins and nature, we are still much in the dark. It is generally held to be a disease of advancing age. This and its rising incidence, an increase parallel with the rising proportion of the aged population, naturally led to the assumption of a direct link with aging, and to an association with the aging process. All of this has only added to the already existing confusion regarding this disease.

In a recent publication we discussed current misconceptions about "senile emphysema" and drew the following conclusions:

1. In the aged, emphysema clinically is not a prevalent disease.

2. It is clinically no different in old people than in the younger age groups.

3. The changes occurring with aging of the lungs and chest are now wrongly identified with emphysema.

To test the validity of these conclusions we have been conducting a clinical study in a large geriatric institution. We will here present and discuss the preliminary findings.

Nature of the Study

This strictly clinical study is intended as an analysis of the prevalence and the distinguishing features of emphysema in the aged. It is in progress at the Francis Schervier Home and Hospital for the Aged. Of 420 men and women residents, the majority (88 per cent) are admitted to the home in so-called normal health for their age. A minority (12 per cent) are admitted as patients to the hospital division. Their age and sex distribution are shown in the following table which also includes our findings.

In each case we included a detailed clinical history and complete physical examination, particularly emphasizing the study of the chest. Periodic x-ray films of the chest were available and it was possible to review serial films often extending over 8 to 10 preceding years. Supplementary clinical laboratory data were obtained when required and in selected cases vital capacity and timed vital capacity studies were included.

Findings and criteria: As the table indicates, we found 18 cases of clinical pulmonary emphysema. These could be readily distinguished

*The Seventh Howard Lilienthal Lecture presented at the annual meeting, New York State Chapter, American College of Chest Physicians, New York City, May 27, 1957.

from changes in the lungs and chest attributable to aging, designated here as "senile lung."

The diagnosis of emphysema was made on the basis of accepted clinical criteria familiar to all. These were the usual symptoms and signs of bronchial obstruction. Clinically manifest emphysema in these aged men and women appeared in no way different from that of younger people. It is also noteworthy that of these 18 cases, 15 were men, indicating a marked sex predilection. Emphysema is predominantly a disease of men regardless of age.

In contrast to this, women showed a marked tendency toward changes in the lungs and chest due to aging, namely "senile lung." We do not consider that the features of "senile lungs," to be described below, constitute a disease entity. Clinically the aged women and men showing these features have practically no symptom or sign of pulmonary disease. Their lungs are quite efficient for their age, especially within the increasingly restricted range of activity which naturally goes with progressive aging.

The diagnosis of "senile lung" was made only in the absence of symptoms and signs pertaining to obstructed breathing and hyperinflated lungs and when physical signs that we now consider normal for old men and women were present. These are:

On inspection, the upper part of the chest may or may not appear distended and the lower halves may appear contracted, depending upon the degree of stooped shoulders. The chest as a whole, however, is *not* overdistended.

On percussion hyperresonance of variable degree may be found. It appears to be restricted to the upper anterior part of the chest.

Auscultation: The outstanding clinical feature appears to us to be the type of breathing. It is quiet, faint, shallow, seemingly effortless, and of a slightly accelerated rate. Very few if any rhonchi are heard. This contrasts rather vividly with the slower labored and more noisy breathing of the emphysematous aged patient. On inducing a cough or on exercise, in the case of senile lungs, one can usually bring about short bursts of sharp and almost juvenile breath sounds. We interpreted this as signifying that basically lung function was adequate. On the other hand,

TABLE I

AGE AND SEX DISTRIBUTION OF SENILE LUNGS AND PULMONARY EMPHYSEMA AMONG 420 RESIDENTS OF THE OLD AGE HOME AND HOSPITAL OF FRANCES SCHERVIER, RIVERDALE, N. Y.—1956

Age group	65-69		70-74		75-79		90-84		85-89		90-94		95-99		100		Total	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Total	21	45	32	53	39	93	21	44	19	23	7	7	6	14	—	1	140	280
Senile Lung	—	1	1	4	3	17	3	15	8	17	3	6	3	11	—	1	31	69
Emphysema	—	—	2	2	8	1	3	—	2	—	—	—	—	—	—	—	15	3

in emphysema of the aged, exercise further impairs breathing and exaggerates the previous signs and symptoms of bronchial obstruction.

On fluoroscopy with a maximal effort of breathing, especially with cough, one can elicit fair movement of chest and diaphragms. This we repeatedly confirmed even in those aged who at first seemed to have an almost fixed chest.

The x-ray pattern which we have come to associate with the "senile lung" seemed significant. In a review of nearly two thousand x-ray films of these aged men and women we identified certain suggestive features: A spongy or lacy pattern of the lung fields associated with increased peripheral lung markings and an enhanced contrast of pulmonary markings seems to stand out. The volume of the lung fields appears diminished, due particularly to narrowing of the chest cage in its lower third where the ribs appear to be more closely approximated. By comparison, the heart often appears enlarged. The upper halves of the chest are often vaulted due to stooped posture. It should be emphasized, however, that the senile lung changes were rarely recognizable roentgenographically under the age of 80.

Although we consider these findings as preliminary in nature we think they warrant tentatively the following conclusions:

1. As a clinical entity chronic pulmonary emphysema in the aged occurs far less frequently than is generally assumed.
2. Its clinical features in the aged (physical, fluoroscopic and x-ray signs) are indistinguishable from emphysema in the young.
3. In a considerable proportion of aged women and men, changes are discernible in the chest and lungs which in themselves do not give rise to clinical symptoms and are not associated with the clinical features of emphysema. These are best designated as "senile lungs" (or lungs of the aged).

Our findings therefore essentially confirm the concepts we discussed in a recent publication.[1]

Discussion

A number of points pertaining to our observations deserve special consideration. The preliminary data presented above are naturally limited to changes discernible by our methods of study, which are rather inadequate. By the criteria mentioned we were able to reveal the presence of senile lung changes in only a minority of aged persons examined. There is a need, of course, of correlating clinical, functional and morphological studies in an adequate number of cases, for which we so far have had too few opportunities. We hope to be able in the near future to present a complementary study along these lines.

Regarding the morphologic features of emphysema and "senile lungs" it should be noted that there is a considerable amount of information already available in recent literature. It is rather gratifying to us that our preliminary findings reconcile the seemingly conflicting conclusions (recently reported by Monroe in America and Howell in England) which were drawn from extensive studies of large numbers of autopsies on

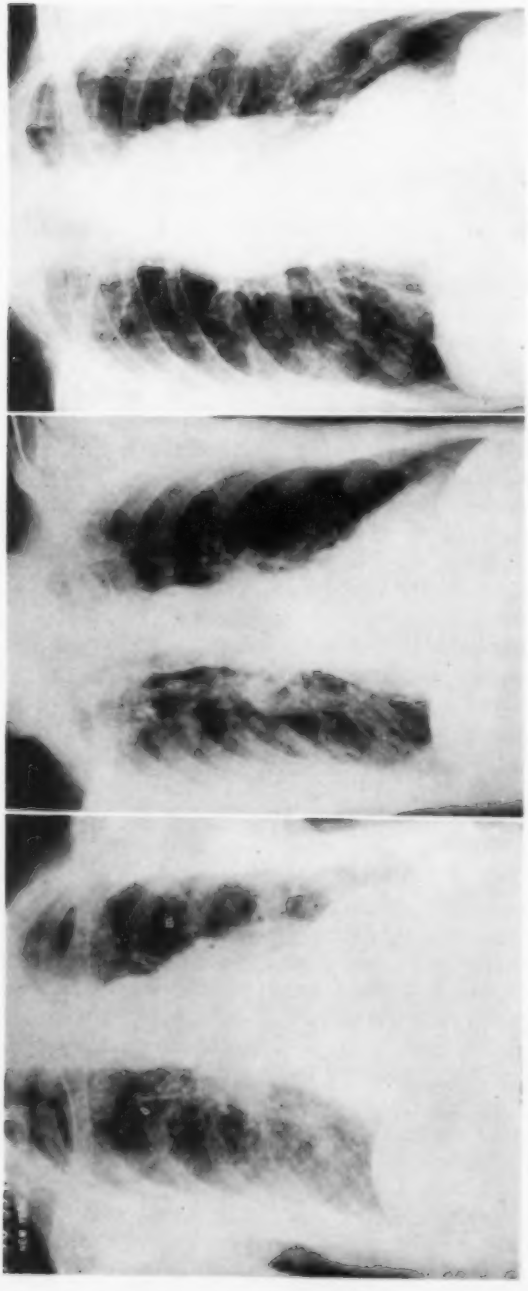

FIGURE 1

FIGURE 2

FIGURE 3

Figure 1: Woman, aged 92, senile lung pattern.—*Figure 2:* Woman, aged 90, senile lung pattern.—*Figure 3:* Man, aged 84, senile lung pattern.

aged patients. Monroe[2] flatly states that emphysema is no more frequent in the aged than in the young. Howell[3] states that the hypertrophic type decreases its incidence with age and becomes rare after 70, when "atrophic emphysema" becomes predominant. It is quite obvious from the discussion of Howell that his description of the atrophic form in the aged is based entirely on interpretation of morphologic features and bears no relationship to any clinical picture. What Howell described as "atrophic emphysema" is in reality what we have defined as "senile lung."

Laennec[1] gave the following description of the morphologic features of the lungs of the aged:

"In very old persons the lungs present some remarkable characters. The calibre of all their vessels seems diminished, they become in some sort exsanguine, the partitions of their air cells appear thinner than natural, on which account their substance, rendered more rare, becomes less elastic, and thus yielding to the atmospheric pressure on opening of the body, they are found to occupy not more than one-third of the cavity of the pleura. They may be said to bear the same relation to the lungs of an adult, that muslin bears to a finer cloth, which is of a texture at once strong and close. These characters are especially observable in the lungs of octogenarians."

This remarkable description of "senile lungs" Laennec included into his introductory chapter on the anatomy and not into his famous chapter on emphysema. By this Laennec implied a sharp distinction between emphysema and senile lungs which we believe applies today just as it did then. In light of this interpretation "senile emphysema" seems to us to be a misnomer and accounts for the high incidence of alleged emphysema in the aged. By the same token the low incidence of true emphysema found by us in this group of aged becomes understandable.

The current classification of chronic emphysema into hypertrophic and atrophic forms has led to the trend of identifying these as obstructive and senile forms respectively. As both are presumed to occur predominantly in patients of advancing age, the obstructive type is usually explained by long protracted bronchial disease, while the atrophic form is linked to the aging process. These concepts have only added to the prevailing confusion, since clinical experience has clearly established certain facts: (1) Chronic pulmonary emphysema is not the disease of advanced age that it is generally assumed to be. A large proportion of the patients are in the 40 to 60 age group and many are even in the 30s. (2) So called "atrophic emphysema" is not uncommonly found in young patients. (3) Pulmonary emphysema occurring as a disease in the aged is just as frequently obstructive in character as in the younger age groups.

The discrepancy between current beliefs and these clinical facts are readily explained on the basis of our concept of the "senile lung" versus "senile emphysema." We note in recent literature, since our publication on the senile lung, that there is now a definite trend to accept

this interpretation. Speaking of the aging lung, Richards[5] most recently emphasized that "the aging normal lung is remarkably adequate and efficient." He discussed a variety of pulmonary conditions now usually spoken of as senile or atrophic emphysema and described these as "pulmonary processes, not aging or senile, but nonetheless truly atrophic and degenerative, that are of importance in the pathogenesis of certain chronic disease stages." The origins of emphysema are still obscure and the terms "atrophic" and "degenerative" do not explain them.

What is now described as "atrophic emphysema" occurs in young and old alike and we do not believe it should be identified as "senile emphysema." The problem of the relationship of senile lungs to emphysema proper remains to be clarified. A little later we shall return to this question.

We found a rather low incidence of clinical emphysema among the aged.* This should not come as a surprise, because it is generally recognized by experienced clinicians that the vast majority of patients with chronic progressive emphysema do not reach old age, especially the old age of today. Of course, some do survive and the cases of emphysema we found were mostly over age 70 and most of them had a fairly long history of pulmonary disease.

Our observations so far indicate that as a rule clinical emphysema does not begin in the aged. By this we do not wish to imply that aging plays no role in the progression of emphysema. Indeed the contrary may be assumed. Chronic emphysema is related to the *exhaustion of pulmonary reserves* by repeated occurrences of a variety of bronchopulmonary diseases

*It should be noted that this group of aged was subject to pre-admission examination and that most of those who were admitted were apparently healthy; hence this should be considered as a selected group.

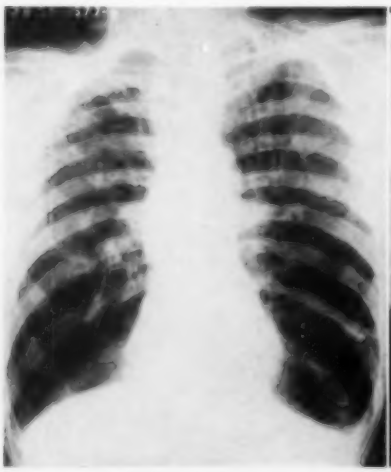

FIGURE 4

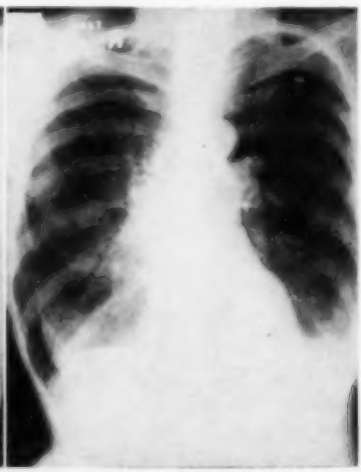

FIGURE 5

Figure 4: Man, aged 87, emphysema.—*Figure 5:* Woman, aged 81, emphysema.

during the patient's life. As a rule the process is gradual and most patients reach at least middle age before they suffer from the symptoms and signs of pulmonary insufficiency recognizable as clinical emphysema. In a few instances the advance is so gradual as to permit some to survive even to age 75 and over.

We found the greatest number of "senile lung" changes in women. Considering that clinical emphysema is known to occur 5 to 10 times as often in men, the predominance of senile lung changes in the aged woman is noteworthy. Special mention should be made of a few observations. First the senile lung changes we found occurred mostly above the age of 80; only rarely below this age. More women than men reach the ninth decade. Furthermore most men over age 80 in this study gave histories of physically active lives and were in fine physical state for their age; on the other hand of the women studied, a large number had never led strenuous physical lives, and progressive aging inclined them to even less activity. We inescapably gained the impression that in the aged who had led physically active lives the involutional lung changes were less marked than in those who had not. Indeed, enforced idleness seemed in a few instances to have accelerated senile pulmonary changes.

From the clinical experience related above, we were led to conclude that functional disuse is probably the most important factor in the pathogenesis of the atrophy of the "senile lung." This conflicts with the prevailing concept of the "atrophy of abuse" which relates emphysema to continued stress on or abuse of the elastic structures of the lungs.

Based on our concept of "atrophy of disuse" it seems that a new approach to the therapy of emphysema has been made. Recently Bickerman[6] stated: "If disuse atrophy plays any part in the pathogenesis of 'senile emphysema,' as has been suggested by Rappaport and Mayer, graded respiratory exercises adapted to the exercise tolerance of the patient will result in clinical improvement and will arrest further deterioration." Accordingly, Barach has been treating emphysema with apparent success employing a program of walking while the patient breathes 10 liters of O_2 per minute, a therapeutic exercise calculated to build pulmonary reserve. While accepting our concept of "disuse atrophy," these clinicians apply it to emphysema in general. If the reported results of this new therapy prove to be correct they may shed light on the relationship between the aging lung and emphysema.

Relative to this we have made some observations indicating that aging may aggravate preexisting emphysematous changes and precipitate the onset of clinical emphysema. Particularly among patients who develop clinical emphysema during advanced years we may be dealing with instances where senile lung changes have aggravated the progressive decline in pulmonary reserve. In a few patients with marked senile lung changes, we observed the occurrence of an acute emphysema-like syndrome which was precipitated by intercurrent illness associated with respiratory embarrassment. Chief among these predisposing factors

were pulmonary congestion of cardiovascular origin, trauma leading to prolonged bedridden state, and a sudden respiratory infection of otherwise harmless nature, such as mild bronchitis. In these cases "senile lung" changes may have served to contribute to the evolution of "clinical emphysema." Perhaps in such cases treatment capable of delaying the progress of the senile lung changes could account at least temporarily for improvement in the patient's condition.

SUMMARY AND CONCLUSIONS

Preliminary findings in a clinical study of emphysema in aged men and women have yielded substantial support of the validity of our concepts of "senile lung" versus "senile emphysema." Aging is associated with changes which result in the senile lung. In our study this change became clinically demonstrable particularly after age 80 and predominantly in women. We found it rarely recognizable before that. However, not all persons show this change, even at this advanced age. In the aged who have led a life of vigorous activity, senile lung changes, particularly in men, appear to be delayed or absent. "Atrophy through disuse" probably plays a role in the changes of the "senile lung."

The term "senile emphysema" appears to us to be a misnomer. The "senile lung" does not manifest itself clinically as emphysema, nor is the latter a common disease among the aged. Clinical emphysema presents the same features in the aged as in the young. In aged emphysematous people the clinical signs and symptoms of obstructive breathing are present and the thorax is overdistended. In the truly senile state, the chest and lungs show loss of structure and contraction in volume, but their functions appear quite suffcient for these aged people with their reduced activities. In some instances "senile lung" changes may predispose to a late and rapid onset of emphysema under such pathologic conditions as congestive failure or bronchopulmonary infections, which tend to increase the functional burden upon the heart and lungs.

RESUMEN Y CONCLUSIONES

Los hallazgos preliminares después de un estudio del enfisema en hombres y mujeres de edad avanzada, han dado respaldo sólido a la validez de los conceptos de "pulmón senil" en lugar de "enfisema senil." Al envejecimiento acompañan cambios que viene a constituir el pulmón senil. En nuestro estudio este cambio se hizo demonstrable clínicamente especialmente después de los 80 años predominantmente en mujeres. Rara vez los reconocimos antes de esta edad. Sin embargo, no todas las personas muestran este cambio aún a este edad avanzada. En los ancianos que han llevado una vida de vigorosa actividad, las alteraciones seniles, especialmente en los hombres, parecen ser retardadas o ausentes. La "atrofia por falta de uso" probablemente desempeña un papel en las alteraciones del "pulmón senil."

El hombre "enfisema senil" nos parece que es mal aplicado. El "pulmón senil" no se manifiesta por sí como enfisema, ni es este último una enfer-

medad común entre los viejos. El enfisema clínico presenta las mismas características en los jóvenes y en los viejos. En los ancianos enfisematosos, los signos clínicos y los síntomas de respiración obstruída se presentan y el tórax está sobre-distendido. En el estado senil verdadero, el tórax y los pulmones nuestran pérdidas estructurales y de la contracción del volumen, pero su función parece bien suficiente para estas gentes de edad con reducidas actividades. En algunos casos el "pulmón senil" por sus cambios predispone a un principio tardío y rápido en evolucionar del enfisema cuando hay insuficiencia congestiva o infecciones broncopulmonares que tienden a aumentar la carga funcional sobre el corazón y sobre los pulmones.

RESUME ET CONCLUSIONS

Les constatations préliminaires d'une étude clinique de l'emphysème chez les personnes âgées ont apporté un argument solide en faveur de nos conceptions du "poumon sénile" par opposition à l'emphysème sénile." La senescence a pour conséquence des altérations qui provoquent le poumon sénile. Rans notre étude, ces lésions purent être mises cliniquement en évidence, particulièrement après l'âge de 80 ans et surtout chez les femmes. On peut difficilement les reconnaitre avant cet âge. Cependant, toutes les personnes même très âgées ne présentent pas obligatoirement de telles lésions. Chez les vieillards qui ont mené une vie très active, les altérations pulmonaires séniles, surtout chez les hommes, semblent reculer leur apparition ou être absentes. "L'atrophie par non-emploi" joue probablement un rôle dans les lésions du "opumon sénile."

Le terme d'"emphysème sénile" ne nous semble pas heureux. Le "poumon sénile" ne se manifeste pas cliniquement comme un emphysème, cette dernière affection n'étant d'ailleurs pas une maladie commune chez les gens âgés. L'emphysème clinique présente les mêmes caractéristiques chez les personnes âgées que chez les jeunes. Chez les gens âgés emphysémateux, les signes cliniques et les symptômes d'obstruction respiratoire existent et le thorax est distendu. Dans la véritable condition sénile, le thorax et les poumons se présentent avec une diminution de leur texture et avec une contraction de leur volume, mais leurs fonctions semblent cependant suffisantes pour ces personnes âgées dont l'activité est réduite. Dans quelques exemples, les altérations dues au "poumon sénile" peuvent prédisposer à l'établissement ultérieur et rapide de l'emphysème à l'occassion de conditions pathologiques telles que les troubles congestifs et les infections bronchopulmonaires, qui tendent à augmenter le retentissement fonctionnel sur le coeur et les poumons.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

Vorläufige Ergebnisse einer klinischen Untersuchung über das Emphysem bei betagten Männern und Frauen ergab eine wesentliche Bestätigung fü die Stichhaltigkeit unserer Auffassung von der "senilen Lunge" gegenüber dem "senilen Emphysem." Das Altern ist verknüpft mit Veränderungen, deren Ergebnis die senile Lunge ist. Bei unserer

Untersuchung liessen sich diese Veränderungen klinisch nachweisen besonders nach einem Alter von 80 Jahren und in erster Linie bei Frauen. Wir fanden, dass sie selten zu erkennen sind vor diesem Zeitpunkt. Jedoch zeigen nicht alle Personen diese Veränderung, selbst nicht in so vorgerücktem Alter. Bei solchen bejahrten Menschen, die ein Læben tatkräftiger Aktivität geführt haben, scheinen senile Lungen-Veränderungen, besonders bei Männern, zu fehlen oder verzögert aufzutreten. "Atrophie durch Nicht-Gebrauch" spielt wahrscheinlich eine Rolle bei den Veränderungen der "senilen Lunge."

Die Bezeichnung "seniles Emphysem" scheint uns eine falsche Benennung zu sein. Die "senile Lunge" manifestiert sich klinisch nicht als Emphysem, noch ist das letztere eine häufige Erkrankung unter alten Menschen. Das klinische Emphysem biete die gleichen Eigenheiten im Alter wie in der Jugend. Bei alten emphysematösen Menschen liegen die klinischen Zeichen und Symptome der stenotischen Atmung vor, und der Thorax ist überdehnt. Beim echten senilen Status zeigen Brustkorb und Lungen einen Verlust an Szruktur und Kontraktion des Volumens, aber ihre Funktionen erscheinen völlig ausreichend für solche alten Menschen mit ihrer herabgesetzten Leistungsbreite. In gewissen Fällen können die Veränderungen einer "senilen Lunge" praedisponieren zu einem späten und raschen Beginn eines Emphysems unter pathologischen Bedingungen so wie Herzversagen durch Stauung oder bronchopulmonale Infektionen, denen die Tendenz inne wohnt, die funktionelle Belastung für Herz und Lunge zu vermehren.

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Pathologic Findings in Benign Pulmonary Histoplasmosis*

Preliminary Report—Part II†

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Another case will be given where the fibrosis was extremely heavy—sometimes the cavity walls measured 2-3 cm. in thickness.

S. R. B. 10 No. 23,637. The patient was a 58 year old housewife of New Madrid, Missouri. She gave a history of "virus pneumonia" in 1951 lasting two to three weeks. Following this she complained of gastric disturbance and was examined for gall bladder disease but an x-ray of the chest caused the private physician to make a diagnosis of tuberculosis and recommended admission to the hospital for treatment. The x-ray film revealed a dense infiltration throughout the right lung field with multiple areas of cavitation. No sputum examinations were recorded up to this time.

In January 1953 there was another attack of "virus pneumonia" and the patient was admitted to the hospital on February 23, 1953. At this time she gave a history of malaise, loss of weight (13 pounds), cough which was sometimes productive, and once in February 1953 the sputum was streaked with blood. In addition there was anorexia, nightsweats and fever. There had been a recurrence of the gastric symptoms with pain in the right upper abdomen but a complete gastro-intestinal workup revealed nothing. The right upper lung field was as previously described. On admission there was a dyspnea, temperature of 99.4, pulse of 120, and respiration of 20. The gastro-intestinal symptoms had disappeared by this time.

The physical examination was essentially negative except for the chest where there were many fine rales on auscultation in the right upper half and mid lung field (Figs. 36 and 37).

The laboratory examination revealed a completely negative tuberculin test, fourteen consecutive negative sputum examinations for acid fast bacilli even though there was an expectoration of 40 to 50 cubic centimeters of purulent to mucopurulent sputum. Two cultures of sputum were also negative for acid fast bacilli.

Three bronchoscopic examinations for acid fast bacilli were negative on smear and culture as well as for cancer cells. Six sputums were also negative for cancer cells. Due to a fluctuating temperature a therapeutic trial of one gram streptomycin three times a week and twelve grams of PAS daily was begun on April 1, 1953. The temperature receded from around 101 degrees to near normal after the antibiotics were given but around July 1, 1953 streaking of the sputum was noted again and a pneumoperitoneum of 700 cubic centimeters was begun on July 4, 1953. At this time 400,000 to 800,000 units of penicillin was administered.

Despite the slight clinical improvement in March there was a progressive increase in symptoms, her general condition declined and the x-ray films showed a progression of the disease. At this time the skin test for histoplasmosis was found positive but the skin test was negative for blastomycosis and coccidioidomycosis. Serum was sent to Dr. Furcolow for complement fixation test which was reported positive on August 1,

*From the Missouri State Sanatorium. We are deeply indebted to Dr. Charles A. Brasher, Medical Director, for unreserved support in this work.

It was the privilege and pleasure of one of us (S) to be accorded the courtesy of members of the Armed Forces Institute of Pathology, in Washington, D. C., where many valuable suggestions were made that helped to orient us in our studies. We are particularly grateful to Capt. Silliphant, Director of the Institute, and to Dr. S. H. Rosen, of the Pathological Department of Chest Diseases.

**Director of Research, Pathology and Allied Sciences.

†Presented in brief before the Chicago Pathological Society, May 13, 1957, and in full at the Am. Soc. Clin. Path. at New Orleans, Oct. 2, 1957.

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A few specimens were from the Pathology Department of St. John's Hospital and Springfield Baptist Hospital, Springfield, Mo., where D. G. and F. C. are pathologists.

1953. In view of the fact that the tests for histoplasmosis were positive and all other tests were negative, the diagnosis pointed to histoplasmosis. Sputum cultures were ordered for Histoplasma capsulatum and on August 20 and 26, 1953, Dr. Furcolow reported positive growth of that microorganism on culture media and the development of disease in mice after inoculation with concentrated sputum. At a later time many positive cultures were obtained.

In view of these findings she was brought to the conference on August 9, 1953 and an exploratory operation was recommended. Accordingly on September 25, 1953, complete pneumonectomy was performed by Dr. Polk and his assistants.

A pathological report was as follows: The gross specimen consisted of resected right lung which weighed 520 grams and had been fixed in formalin. The upper half presented marked thickening of the pleura and had been resected with attached parietal pleura. In some places the pleura measured 2-3 cms. in thickness and had a dense fibrotic make-up which in some places had the consistency of cartilage. On section all the upper half of the lung presented an intercommunicating irregular cavity. The inner surface was rather smooth, grayish in color and transversed by obliterated thrombosed blood vessels and cords of broken-down bronchi. The wall of the cavity was light gray with areas of anthracotic deposition and the tissue everywhere was very dense. Beneath the lower margin of the thickened pleura there was revealed several patent fistulous openings which communicated with the cavity. There were numbers of enlarged peribronchial and hilar lymph nodes which generally were of gray to black color with only occasional tubercle-like formation around the periphery. There was a 1 cm. sized, rather thin-walled cavity in the base of the lower lobe which contained purulent grayish colored exudate. On section of the rest of the lung the parenchyma was doughy in consistency but presented no grossly demonstrable lesions (Figs. 38 and 39).

Microscopic examination of a number of sections from the tissue bordering on the large cavity in the upper lobe revealed no functional lung parenchyma. The area lining the cavity presented on inner aspect, much cellular detritus and degenerating reactive cells of various types. This over-lay an area of acidophilic staining hyloid material in which there were relatively few reactive cells and the true nature of which was not apparent. Just beyond this there was a mixed chronic type of cellular reaction which was made up mostly of plasma cells, fibroblasts, mononuclear macrophages and also a few multinucleated foreign body giant cells. Beyond this area there was

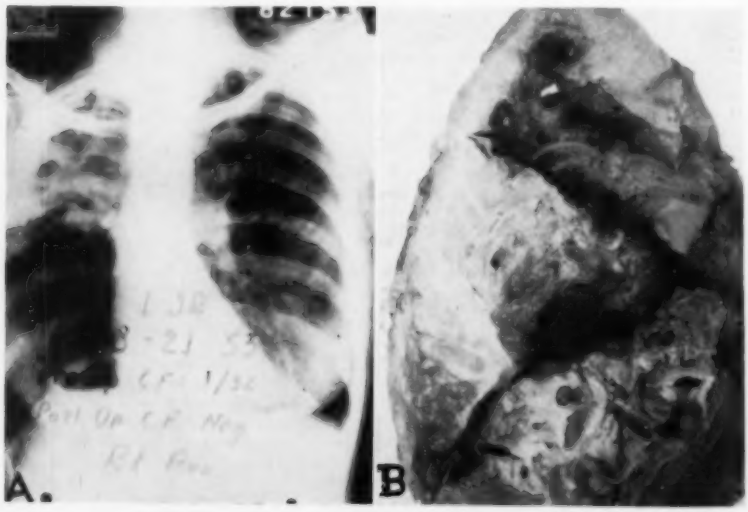

FIGURE 36 FIGURE 37

Figure 36: (A) Roentgenogram of S. R., B10, No. 23,637, taken on August 21, 1953. Note destroyed right upper lobe.—*Figure 37:* (B) Sagittal section of upper lobe of lung removed on September 25, 1953, showing extremely thick-walled cavities with no pyogenic membrane.

a rather compact fibrocystic reaction in which there were foci of chronic reactive cells and also among which there were regenerating alveolar and bronchiolar structures. Occasionally a single and conglomerate tubercle-like formation was observed within this area and the reactive components of which were usually of fibrous and epithelioid cells as well as one to several multinucleated foreign body giant cells. Occasionally within the giant cell there was observed an irregular shaped refractile body which morphologically appeared to be a foreign body rather than ingested bacteria. In two sections

FIG. 38

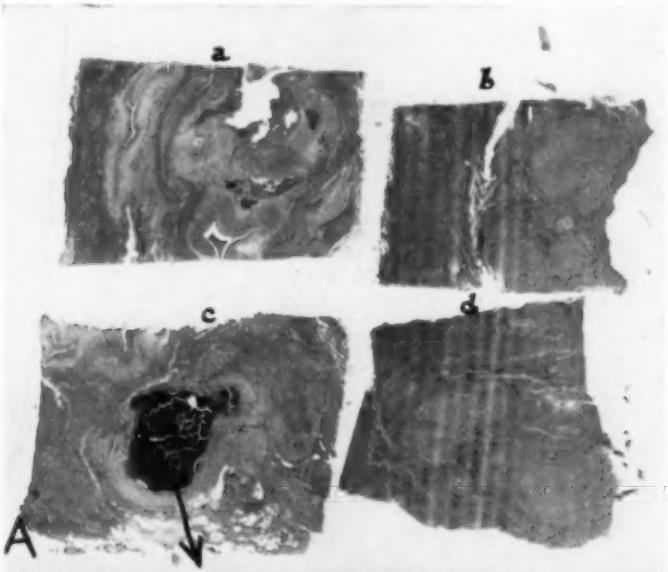

FIG. 39

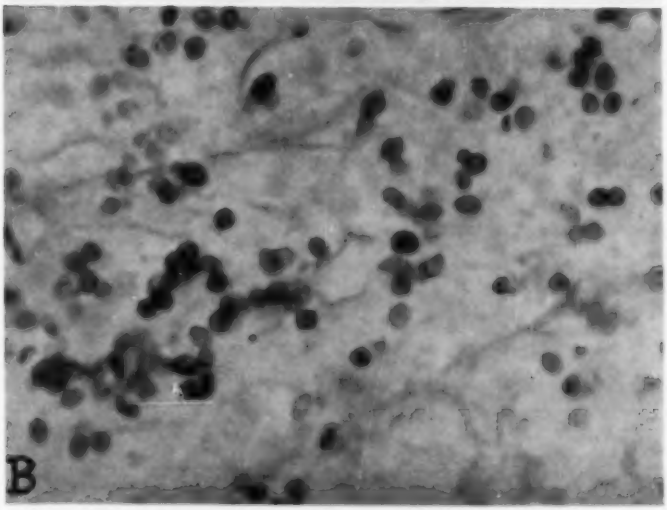

Figure 38: (A) Sections "a," "b," "c," "d," made from encapsulated lesions removed and stained in 1956. H. & E. × 4.5—*Figure 39:* (B) Microscopic photograph of yeast bodies found in the "c" lesion of Fig. 38. G. M. S. stain × 3200.

there were observed secondary bronchi which presented thickening of their walls secondary to marked secondary chronic inflammatory reaction. In two there was definite erosion of the bronchial mucosa and extension of the inflammatory reaction into the submucosal levels. The lesion was definitely of granulomatous type but not typical of mycobacterial infection. Sections of accompanying lymph nodes showed in two, several fibroepithelioid tubercle formations in which there were from one to several multinucleated foreign body cells of the same type seen in the lung lesions. The lymphoid stroma otherwise was moderately hyperplastic. No inclusion bodies of the Histoplasma type were observed within the reactive cells.

Cultures initiated from the lung lesions presented colonies which were morphologically suggestive of Histoplasma capsulatum. Acid fast stains and PAS stains did not demonstrate the presence of Microbacterium tuberculosis or any fungal organisms. Diagnosis: Right pneumonectomy for chronic cavitary granulomatous pneumonitis caused by Histoplasma capsulatum based on bacteriological and serological findings.

Due to the uncertainty of the staining methods used up to this time, a complete re-examination of the gross and microscopic specimens was made in January, 1957. Since the special stains used did not reveal any typical findings of H. capsulatum and since the more recent observations and technical advancement had changed the method of approach in examination, the gross specimen was re-examined for encapsulated caseous and calcified foci, cut and stained by the G. M. S. technic. About four encapsulated lesions were removed and examined for yeast. The result was the finding of a large number of yeast bodies typical of H. capsulatum in most of the specimens as well as a few forms in the wall of the cavity.

This completed the search for the etiological agent and established the fact that every test for the presence of histoplasmosis was positive and practically every test for other conditions was negative.

The final diagnosis was, therefore, acute and chronic fibro-ulcerative, fibrocaseous nodular and infiltrative histoplasmosis.

It is worth noting that after two re-admissions to the hospital and re-examinations, the patient has up to now, July 1957, not revealed any exacerbation of her disease. This is five years after her operation.

A sixth group was bronchiectasis. Although bronchiectasis may be caused by many infectious agents, histoplasmosis may be one of these agents, as shown in one of the cases. In one case a culture of H. capsulatum was obtained from a specimen of the bronchial wall. Everything else was negative, but because of this positive culture a careful search was made of the tissue and every encapsulated lesion was excised and stained by the G.M.S. stain. Many parasites were found in the encapsulated lesions but only a few were found in the wall of the bronchiectatic cavity. Once again it showed the predilection of these parasites for encapsulated caseous foci. A more complete report on bronchiectasis will be given in a separate study.

The seventh group may be considered as a pleuritic involvement with effusion, not greatly unlike that seen in tuberculosis. There was one case in which the effusion contained Histoplasma capsulatum, and without the presence of the parasites it could not be distinguished from tuberculosis.

Finally, there was a mixed up group that includes many of these various types of lesions because in practically every case two or more of these various types of pathology could be found. There were sometimes calcific, and chronic fibroid lesions associated with acute caseous foci and with cavity formation. In most of the chronic forms there were found encapsulated caseous foci in which numerous parasites were found. It may be stated that there was nothing found that simulated microscopically the tuberculous caseous pneumonia.

Probably one of the most difficult distinctions—in fact, impossible without the parasites of both diseases—is to tell when tuberculosis and histoplasmosis exist together. In four cases, tuberculosis was diagnosed first

because of the acid-fast bacilli, but after long drug treatment the disease continued after the acid-fast bacilli had long since disappeared. Since this combination is so important, the four cases will be briefly summarized.

A. R. W., B. 6, was a 35 year old painter. The skin test was strongly positive for histoplasmosis and the tuberculin skin test was weakly positive. The complement fixation was weakly positive with one antigen and negative with the other. Sputum smears were positive for acid-fast bacilli on numerous occasions. All cultures and mouse inoculations were negative for histoplasmosis. The sputum smears finally turned negative for tubercle bacilli, after which a surgical resection was performed. On the P.A.S. stains of prepared sections there was granulomatous tissue present with many histiocytes containing many suspicious "cherry colored" bodies. These were not considered diagnostic of histoplasmosis, but when four or five typical forms that showed birefringence were found on the Gomori stain, the diagnosis of histoplasmosis was made. Segmental resection of the left upper and wedge resection of the lingula removed all apparent disease up to the present time.

E. S., B. 15, No. 23,056, was a 50 year old truck driver. The skin reaction was weakly positive for histoplasmosis and strongly positive for tuberculosis. The complement fixation was weakly positive. At the beginning all sputum smears were positive for acid-fast bacilli, but turned negative and remained negative, yet the disease continued until the whole left lung was destroyed. Pathological findings revealed a typical appearing primary type of tuberculous lesion; however, it was called a reinfection complex on gross inspection. On microscopic study, the lesions contained many bony rings and appeared more like a true primary tuberculous complex. In these lesions were many yeast bodies that pointed strongly to a primary complex of histoplasmosis. This case seems to represent, therefore, a very old histoplasmosis that was superimposed with tuberculosis, and the two diseases ran parallel until the drug treatment seemed to limit the progress of the tuberculosis, and the surgery ended the threat of both diseases, temporarily at least.

O. W., B. 24, No. 25,388, was a 58 year old farmer with a weakly positive skin test for both histoplasmosis and tuberculosis. There was a strongly positive complement fixation test with both antigens. Six sputum smears were positive for acid-fast bacilli, but after a course of drug treatment, the acid-fast bacilli disappeared from the sputum. Numerous cultures were positive for histoplasmosis and the complement fixation continued positive, many times as high as 1:256 dilution. The whole right

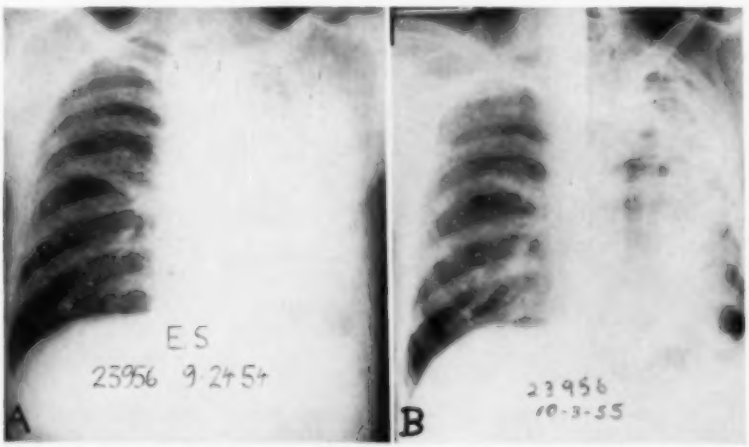

FIGURE 40 FIGURE 41

Figure 40: (A) Roentgenogram of E. S., B15, No. 23,956, taken on September 24, 1954, showing a consolidated left lung.—*Figure 41:* (B) The same as Fig. 38, taken on October 3, 1955 with a double exposure to show the nature of the lesion on the left. This patient was always positive for a.f.b. and turned negative on antituberculosis drugs.

upper lobe was destroyed and contained a large cavity. A surgical resection was successful, but the patient died later of a coronary thrombosis. The pathological findings consisted of a cavity wall that was more typical histoplasmosis than tuberculosis. There were scattered yeast bodies throughout the cavity wall and in some of the caseous foci, but since no encapsulated lesions were found, the large accumulations of parasites found in so many of the other cases were absent. The reaction was histiocytic, not granulocytic. This case was one in which the two diseases seemed to run parallel, but the tuberculosis was suppressed, either by drugs or by the histoplasmosis. The surgery was successful and the death was in no way caused by either disease, or by the operation.

R. H., B. 25, No. 25,465, was a 33 year old janitor with a positive skin test for both histoplasmosis and tuberculosis. The complement fixation was positive with both antigens. The sputum smear was positive during the early stages of treatment for acid-fast bacilli. All cultures for histoplasmosis, both sputum and pathological specimens were negative. Birefringent yeast-like bodies were found on the Gomori stain. The two diseases were both present in this case, but the acid-fast bacilli disappeared first, either due to the drug treatment, or to the histoplasmosis. A wedge resection of the left upper lobe and a decortication of the left pleural cavity was successful and the patient made an uneventful recovery.

FIG. 44 FIG. 45

FIG. 42

FIG. 43

FIG. 46

FIG. 47

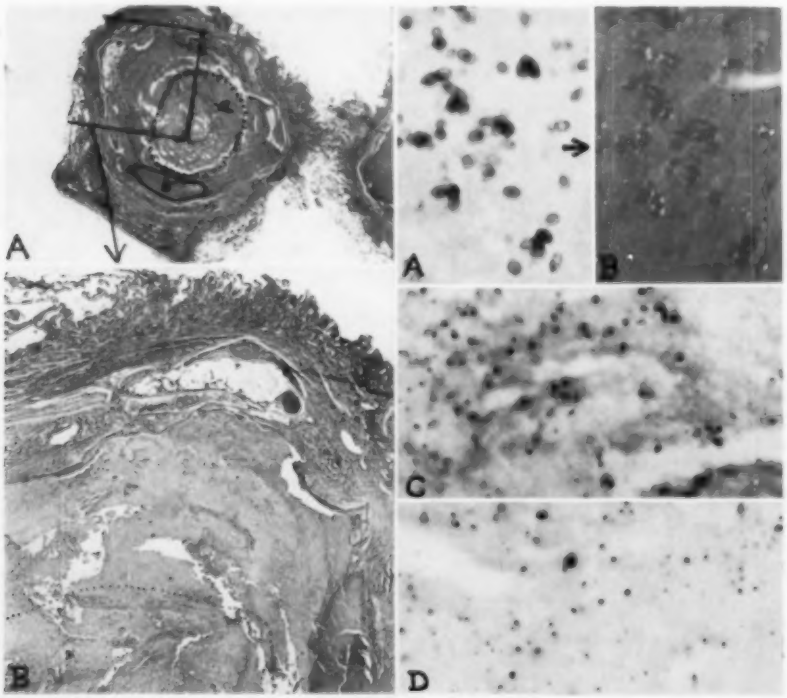

Figure 42: (A) A low power view of a section of a dense parenchymal calcification taken from the resected left lung of patient shown in Figs. 38 and 39. Two areas are outlined in the center of the lesion, one by dots at "a," and another by black line at "b." H. & E. × 4.5.—*Figure 43:* (B) A squared-off area of Fig. 36 showing bony character of lesion. H. & E. × 20.—*Figure 44:* (A) A microscopic view of region marked at "a" in Fig. 40, showing numerous typical yeast bodies. G.M.S. stain × 3200.—*Figure 45:* Polariscopic view of Fig. 42. × 3200.—*Figure 46:* (C) A view of field marked off at "b" in Fig. 40. Note the numerous small dark staining bodies that may be developing into yeast bodies. G. M. S. stain × 3200.—*Figure 47:* (D) Another view of the field of "b" in Fig. 40. G. M. S. stain × 3200.

Another condition that may be simulated by histoplasmosis is sarcoidosis. It must be pointed out, however, that the finding of parasites in a sarcoid-like lesion does not rule out sarcoidosis, nor does it imply in any way that histoplasmosis may be the cause of sarcoidosis. Since the normal expectancy we found in this region of tuberculosis in the presence of active histoplasmosis is 25 per cent, that same percentage at least may be expected in sarcoidosis, Hodgkin's disease, lymphomas, or any other similar involvement. In three cases, however, of proved sarcoidosis, yeast bodies were not found.

It must not be inferred either that the ratio found here will be found elsewhere, especially in places where the histoplasmosis is not endemic. An examination of some of the old tubercles studied many years ago by one of us (S) in an area low in incidence of histoplasmosis has revealed no H. capsulatum in a large number of the stained sections.

Another condition as briefly mentioned that may be produced, is bronchiectasis. Histoplasma capsulatum may be the inciting agent, like many forms of bacterial infection and other conditions leading to bronchial stricture that results in bronchial dilatation and the accumulation of pus in the sacs formed. In such lesions there is much non-specific reaction.

Discussion

Although we have attempted to describe the gross and miscroscopic lesions found in our material as consistently as possible, it is evident that there are still gaps in the pathology of the disease that probably were not found. For example, it is highly probable that many lesions are primary infections with the parenchymal infiltrates and lymph node involvements like those found in tuberculosis. Such lesions, however, would be easier to study during the early stages of the infection. Many of the calcified lesions may have been old primary lesions, but with two exceptions only the parenchymal components were excised so we wouldn't be certain of the complete pathology. Ulcerative bronchitis was not found in any of the histoplasmosis cases, although growth into the bronchi of one case was found. Hematogenous dissemination in the lungs was not found. There probably are other conditions also that were not represented in our material.

One of the big problems, in fact, the most important problem, is establishing a diagnosis of histoplasmosis. Owing to the fact that the disease simulates tuberculosis, sarcoidosis, and other diseases so closely, clinical and x-ray findings are of limited value. With the possible exception of the history, such as occupation and geographic location, clinical and x-ray findings are at no time conclusive. The skin reactions and complement fixation are sometimes helpful. In an endemic area, especially if the individual has been working around decayed and drying organic material such as chicken and pigeon manure, silos, or dry dust, and if there is a strong positive skin reaction and strong complement fixation for histoplasmosis with negative tuberculin, there is strong presumptive evidence of histoplasmosis. Negative findings, however, of any or all of these indicators

do not rule out the disease. The only absolute diagnosis is when a typical culture of the parasite is grown on some or all of various media and when animals are infected and die with the disease. Even under the best of circumstances, however, culture and animal inoculation is only about 50 per cent efficient up to this time in the type of case we have been dealing with. The complement fixation proved to be erratic, since in three clinically positive cases the reaction was negative, and many positives did not have any parasites on culture or in the tissues examined. Salvin[16] suggested that there were at least three antigens. It has been shown that the complement fixation antibodies appear best at the height of the acute disease and that they tend to fade in chronic forms and almost entirely disappear in fulminating cases. McLauren, Beamer and Tuttle[17] have shown that there is not a single antigen, but there is a difference between the whole yeast antigen and the mycelial antigen.

The skin reaction persists much longer. It is more useful, except where the complement fixation is present in high dilutions or the tuberculin positive.

The staining of tissues is one of the best means of establishing a diagnosis. There has been marked progress made in this field recently. Although the H. and E. stain is standard for almost every histopathological method, it stains the yeast parasites little or not at all, and more important, there are calcific rings that simulate the parasite closely. Unless there is an overwhelming infection with large numbers in the macrophages, the parasites will be missed. Although the PAS stain with various modifications was a considerable advance, there is much the same objection to it as to the H. and E. stain. When the macrophages are packed with the parasites rather early in the disease, they may be distinguished easily by the cherry-colored nuclear material surrounded by a capsule which usually stains a similar color. There were no more than four of our cases, however, which we felt with none too much certainty were H. capsulatum based on the PAS stain. One of the principal artefacts that simulate these bodies is the early stage of hemosiderin formation, when the hemosiderin becomes phagocytized in small clumps and appears very much like the parasites. Although there are many substances in the tissues that stain with the PAS stain, most of such artefacts can be separated from anything that resembles the parasite of histoplasmosis.

The Gridley stain has eliminated many of these extraneous factors, but it still is lacking in being able to identify the parasites with regularity.

It should be kept in mind, that a diagnosis of many conditions including tuberculosis may not be definitely established. If artefacts or inadequate findings lead to a diagnosis of histoplasmosis in the absence of other findings, who can dispute the diagnosis? Many "diagnoses" have perhaps been made on artefacts. That is the reason why great care and definite proof must be found before a diagnosis is made. Furthermore, it must be pointed out that parasites are not always found either in tuberculosis or histoplasmosis. Perhaps the average results are not higher than 90 per cent when only *one* section is examined, because one section represents much

less than 1 per cent of each round lesion. Our results were only about 82 per cent.

The methenamine silver stain of Gomori which was originally intended as a glycogen and mucin stain, but was used in identification of yeast parasites by Grocott, has been found to be the best of all tissue stains for identification of H. capsulatum and many other yeast and mold parasites. It is especially useful in identification of H. capsulatum because most of the other yeasts and molds may be identified by some of the other stains.

In performing this test it is well to remember that perfection of technic is most helpful. The purity of the chemicals, the timing of the exposure to these chemicals, together with a well regulated temperature is necessary for good results. It is well for each operator to develop his own technic with great precision and run good control stains for comparison. The procedure may be compared to expert photography in bringing out desirable features.

As a method of control of the various forms adjudged to be yeast bodies, we made use of the polariscopic attachment of the Leitz Dialux microscope to test the birefringence of the parasites. A description of the use of the polariscope in identifying birefringence in the various yeasts has been given by Potenza and Feo.[18] We used this polariscope method after finding the bodies stained by Gomori's method.

It must be pointed out, however, that this is not absolute either, because it is dependent upon proper staining and the presence of the polysaccharide which is reduced to the aldehyde and which in turn reduces the methenamine silver to metallic silver. A more complete discussion of this method will be given at a later time, but it may be stated here that there are numerous artefacts that have to be considered and eliminated, much like the staining of tubercle bacilli with the acid-fast stain. We feel, however, that the Gomori (G.M.S.) method compares as favorably in histoplasmosis as the acid-fast stain does in tuberculosis, especially when all the control methods are carried out and when checked by the polariscopic findings.

It appeared to us that we were able to follow the disintegration of the macrophages and the parasites they contained, better with the Gomori stain than any other. Nevertheless, as the disintegration progressed the small black bodies that perhaps represented the parasites seemed to become smaller. There came a time when it was impossible to tell these bodies from carbon and iron pigment. We were impressed with the possibility that most of the parasites appeared to be destroyed by the macrophages, but after the macrophages themselves became destroyed some of these small spore-like bodies or residual nuclear portions of the parasites still may have retained life, and after months, and even years, began to grow in encapsulated caseous and calcified foci. Otherwise, how could a growth occur in a densely encapsulated and calcified lesion?

Another thing was that the evolution of these granules seemed to progress from approximately one micron in diameter or even less, according to standard measurement, through various sizes, up to the usual size of three to five microns. Birefringence could rarely be identified in any forms

less than one micron in diameter, but a few cases showed birefringence in forms approaching 0.5 μ in diameter. In a subsequent study birefringence was found in forms of 0.3 -0.4 μ in diameter indicating the presence of a polarizing substance.

There are other reasons for suspecting that this "underground" aspect exists. As mentioned before, a well encapsulated lesion is practically impervious to outside elements. Only ions can penetrate the capsule, but no blood elements or parasites such as H. capsulatum can enter until blood vessels penetrate one or more decades later. Yet in all well encapsulated calcified and even ossified lesions of the series, parasites were found almost exclusively in the central caseous and calcified area and rarely in the area where the capillaries have penetrated and eroded away the capsule and laid down bone and bone marrow.

After an unknown interval of time, the small black granules appear to enlarge and increase in numbers reaching sizes up to 3 or more microns; clusters appear, and finally large numbers of vigorous yeast forms appear in the depth of the heavily encapsulated caseated and calcific nodules.

Numerous other artefacts than those mentioned have bothered us considerably, but we have been able to overcome most of them. Such things as fat droplets, lipoid bodies, and degeneration vacuoles can be eliminated with experience. Various crystalline substances which cause birefrigence have also interfered with the polariscopic examination, especially in the unstained specimens. We found that the methenamine silver seemed to destroy most of the crystals that cause interference. Checking the typically egg-shaped yeast bodies with birefringent characteristics shown on the polariscope, especially if there was a typical "Maltese Cross" formed, came about as near to establishing the presence of H. capsulatum as anything outside of growing the parasites. Besides it will find about 40 per cent more positives than the present culture methods.

It is our feeling that about 10-15 per cent of the cases were histoplasmosis but we are unable to find the yeast bodies in the material studied. It is sometimes quite difficult to find the parasites in some cases and then there may have been only a few. In a few cases they were never found. One thing certain is that caseation seems to be the indispensable medium for the propagation of the yeasts in encapsulated lesions. It seems reasonable to suspect that some irritant causes the expanding of the circumscribed lesions, but unless a caseous focus develops no parasites are demonstrable. It is also possible that the parasites may be present in forms that we have not yet been able to recognize. The complete evolution of the parasites is not yet known and until then we must speculate especially with regard to the small spore-like bodies that seem to develop in the caseous areas. In some cases even after several sections at different levels of the block, typical yeast bodies were not found but it must be considered that in a 2 cm. lesion a 6 micron section is only about 1/2000ths of the whole specimen. In none of the specimens therefore did we examine more than 1/10th of one per cent of the total specimen saved.

There are still many unknowns in the histoplasmosis problem, and many

needs that must still be supplied. First of all is regarding the culture medium which in our material only grew at the maximum about fifty per cent of the known positive specimens. Another need is to explore the evolution of the parasite within the lesions of the body. There seems little doubt from studying this material carefully that the yeast form undergoes a change as the macrophages engulf the yeast and apparently destroy them. But by the silver stain there are many small blue-black dots that remain in these old destroyed phagocytes. It is reasonable to suppose that these bodies may be microspore formations that lie dormant for long periods of time after they are entrapped within the central part of a lesion and remain there for months and years before they are able to develop back into the typical yeast formations. A series of transition forms have been followed in all but a few of the cases, from these small blue-black dots through to micron size round bodies up to the typical yeast-like forms which become unmistakable from one and one-half microns on up.

While it is not intended to give any extensive clinical findings there are some that may be mentioned in passing. Pneumonia was quite frequent in our series of cases and it usually was diagnosed virus pneumonia because there was apparently no microorganisms found. Another thing was the vague and indefinite gastrointestinal complaints, sometimes referable to the liver and gall bladder and other times to the stomach. There were several ulcers of the stomach that were excised. Whether that had any relationship to the tendency to develop histoplasmosis is, of course, not determinable at this time. In the cases that we have reported we have found the histoplasmin skin test of greatest value outside of culturing and staining the microorganisms. The complement fixation test is dependable in the higher dilutions where it is considered to be diagnostic. Among the patients that we have described in our series of cases, chicken raising or farming of some kind where chickens have been raised has been a common denominator in many cases.

In retrospect, it seems that the disease of histoplasmosis is one that parallels tuberculosis very closely, although there are differences which have been mentioned but which will not be discussed at this time. There is apparently elaborated a toxic substance that produces the skin reaction in infected people, as well as antigens that produce complement-fixing antibodies. It is possible that there are more than one of these antigens and that they may differ qualitatively and quantitatively under different circumstances and at different times. That may help to explain the erratic findings of the complement fixation reaction in this resected material.

In general, histoplasmosis seems to be much more benign than tuberculosis, but in susceptible people with depressed resistance due to malnutrition, other disease, infancy, old age, or overwork, the disease may develop in varying degrees of acuity and produce pathology, some of which we have attempted to describe. From our present vantage point it would seem that the disease would yield to methods of treatment more readily than tuberculosis, but that parasites are more prone to survive in encapsulated lesions.

It is important to realize that only a small minority of the lesions ever produce active disease, although it appears that histoplasmosis has a long carrier state resembling syphilis, malaria and tuberculosis. At this time it appears that in an endemic area such as ours, the incidence of clinically active histoplasmosis is a great many times less than tuberculosis. The ratio will probably change, however, as tuberculosis decreases, since there is no way at present to control the spread of histoplasmosis as there is tuberculosis.

A question might be raised with reference to length of time the parasites may live in old lesions. In one very old lesion no budding and only the faintest birefringence could be detected in rather poorly stained parasites. In another case the parasites could be followed through faint staining to mere outlines or ghosts. It is felt that the point of viability has passed when budding ceases, staining fades and birefringence disappears. Whether any "spore" forms may exist to perpetuate these forms is not always evident. Recent and unpublished data reveal much more information on this subject.

A word should be said here relative to culturing of H. capsulatum. With the latest technic in two laboratories, only 50 per cent of the known cases of histoplasmosis in our material produced growth on culture media or disease in mice.*

SUMMARY

A preliminary report has been made on the pathologic findings of proved histoplasmosis in 21 circumscribed lesions and sixteen clinically active lesions. In addition, there were three doubtful cases in each group that were thought to be histoplasmosis, but in which no typical parasites could be found.

There were 24 more specimens examined in which histoplasmosis was not found. These served as good controls because they included principally tuberculosis, in which acid-fast bacilli were found and three cases of bronchogenic carcinoma. They were included because of the close similarity in clinical, x-ray or other findings to histoplasmosis.

There were four clinically active cases with both acid-fast bacilli and H. capsulatum.

In addition, three cases of known sarcoidosis as well as many controls of other diseases were stained and examined, but parasites were not found.

There were two series of cases, one including apparently inactive disease of so-called "coin" lesions and the other consisting of clinically active disease.

The pathologic findings were as follows: Group one, centrifugally formed spherical lesions; Group two, encapsulated infiltrates; Group three, caseous nodular lesions resembling caseous tubercles from 1 to 15 milli-

*We wish to extend our thanks to Dr. Michael L. Furcolow and Dr. Howard W. Larsh and their assistants at the U. S. Public Health Service Field Station Laboratory at Kansas City, Kansas, for complement fixation results and for making the cultures during the early part of this study, as well as helping to establish our Mycological Laboratory. Also to Dr. Joseph Guasch for valuable assistance with the photographic work and to Mr. Robert Shackleford for helping in preparing sections.

meters in diameter and fibrocaseous calcific and calcific-ossified lesions; the fourth group was chronic pneumonitis which is thought to be divided into several phases of age development from the histiocytic inltration and early organizing fibrinous pneumonia with histiocytes, to the late granulomatous-type of lesion that simulates sarcoidosis; Group five were the ulcerative types which are divided into caseo-ulcerative (an advanced stage of the caseo-nodular) and the fibroid type of lesions, which ranged from thin-walled, cystic, moderately thick-walled to thick fibrous-walled cavities; the sixth group was pure bronchiectasis that cannot be distinguished in appearance from any other bronchiectasis, but which was found to be a result of infection by H. capsulatum; Group seven was the pleuritic-type which is due to invasion of the pleura by H. capsulatum; an eighth group was a mixture of two or more of the others.

In preparing to make the examinations on this material, an exhaustive study was made of many types of artefacts which were removed or identified by special stains wherever possible.

The stain found best for staining yeast bodies was the Gomori methenamine silver (G. M. S) stain as adapted to the identification of yeast by Grocott.

Of the 16 definitely positive active cases, 14 were cultured and/or inoculated into mice, but only seven were found positive.

The findings were confirmed where possible by the use of the polariscope, as recommended by Potenza and Feo. While not diagnostic it does show the presence of a polarizing substance, probably a polysaccharide.

A theory was advanced for the possible evolution of the parasites in the body from the phagocytized cells in the macrophages to a quiescent spore-like form in the fibroid tissue and later a re-awakening of these spore-like forms (endospores) into active yeast cells at a time varying from months and years to decades. A further elaboration of these possibilities will be carried out in a subsequent work where more discussion will be possible.

RESUMEN

Se presenta una comunicación preliminar sobre los hallazgos patológicos de histoplasmosis demonstrada en 21 lesiones circunscritas y en 16 lesiones clínicamente activas. Además, hubo otros tres casos dudosos en cada grupo, los que se pensó eran de histoplasmosis pero en los que no se encontró el parásito.

En 24 especímenes más que se examinaron no se encontró el histoplasma. Estos sirvieron como control porque se trataba principalmente de tuberculosis en los que se descubrieron bacilos ácido resistentes y en tres casos se encontró carcinoma bronquiogénico. Se inclyen porque tienen gran similaridad clínica, radiológico y por otros hallazgos.

Hubo cuatro casos clínicamente activos con bacilo de la tuberculosis y al mismo tiempo histoplasma capsulátum.

Además, tres casos de sarcoidosis conocida así como muchos controles de otras enfermedades fueron teñidos y examinados pero no se encontraron los parásitos.

Las series de casos fueron dos: una incluyendo los aparentemente inactivos de la enfermedad como los llamados lesiones en forma de "moneda" y la otra, de clínicamente activos.

Los hallazgos fueron como sigue: Grupo 1: lesiones esféricas formadas centrífugamente; Grupo 2: infiltrados encapsulados; Grupo 3: lesiones caseosas nodulares parecidas a tubérculos caseosos de 1 a 15 mm. de diámetro y lesiones calcificadas y calcificadas osificadas; el Grupo 4: era de neumonitis crónica que se cree se divide en diferentes fases de edad de desarrollo desde la infiltración histiocítica y la neumonía fibrinosa temprana organizante con histiocitos hasta a granulomatosis tardía de la lesión que simula la sarcoidosis; el Grupo 5: era de las formas ulcerosas que se dividen en caseo-ulcerosas (etapa avanzada de la caseonodular y el tipo fibroide de lesiones que van desde la de paredes delgadas, quísticas, a las moderadamente engrosadas en la pared y a las cavidades con paredes fibrosas gruesas; el Grupo 6: era de bronquiectasia pura que no se puede distinguir en apariencia de cualquiera otra bronquiectasia pero que se encontró eran resultado de la infección por H. capsulátum; el Grupo 7: del tipo pleural debida a la invasión de la pleura por el H. capsulátum; el Grupo 8: fué una combinación de dos o más de los grupos anteriores.

Al preparar el examen de este material se hizo un estudio agotando las posibilidades de muchos "artefactos" que pudieron quitar o identificar por colorantes especiales cuando fué factible.

El mejor colorante para los cuerpos de esas levaduras fué el de Gomori metenamina plata (G.M.S.) como se adaptó para la identificación de levadura por Grocott.

De los 16 casos francamente activos e identificados, se cultivaron 14 y/o se inocularon en ratones pero sólo 7 fueron positivos.

Los hallazgos fueron confirmados cuando fué posible por medio del polariscopio según lo recomiendan Potenza y Feo. Aunque no es diagnóstico, muestra la presencia de una substancia polarizante que probablemente es un polisacárido.

Se presenta una teoría la sobre la posible evolución de los parásitos en el cuerpo desde la celdilla fagocitada en los macrófagos hacia una forma semejante a esporas en el tejido fibroide y después un despertar de estas formas semejantes esporas (endosporas) hacia las celdillas de levaduras activas en un término que puede variar de meses a años y décadas.

Se llevará a cabo un estudio ulterior de estas posibilidades y se espera poder entonces discutir esto más adelante.

RESUME

Il s'agit d'une communication préliminaire sur la constatation vérifiée d'histoplasmose dans 21 lésions circonscrites et I6 lésions cliniquement actives. Il y eut en outre trois cas douteux dans chaque groupe qu'on attribua à l'histoplasmose, mais dans lesquels aucun parasite typique ne put être trouvé.

Dans 24 échantillons, on ne trouva pas d'histoplasmose. Ils servirent de témoins, constitués par de la tuberculose, avec bacilles tuberculeux

et dans trois cas de carcinome bronchique. Ils furent insérés dans cette étude à cause de létroite similitude des constations cliniques et radiologiques avec l'his toplasmose.

Dans quatre cas cliniquement évolutifs, se trouvaient associés des bacilles tuberculeux et l'histoplasmosis capsulatum.

En outre, trois cas de sarcoïdose connue ainsi que beaucoup d'autres soumis à investigations pour d'autres diagnostics, furent colorés et examinés, mais on ne put mettre en évidence aucun parasite.

Il y eut deux groupes de cas, l'un comprenant les lésions apparemment inactives appelées "lésions en forme de pièce de monnaie" et l'autre consistant en affections cliniquement actives.

Les constatations anatomo-pathologiques furent les suivantes: — Groupe I: lésions sphériques formées de manière centrifuge; — Groupe 2: infiltrats encapsulés; — Groupe 3: lésions caséeuses nodulaires, ressemblant à des tubercules caséeux de I à 15 millimètres de diamètre, et des lésions calcifées fibrocaséeuses, et ossifiées. Le quatrième groupe comprenait une pneumonie chronique qui, pense-t-on, devait être divisée en plusieurs phases de développement, depuis l'infiltration histiocytique et une pneumonie fibrineuse s'organisant précocément avec histiocytes, jusqu'au dernier type granulomateux de lésion qui simule la sarcoïdose. Le groupe 5 était composé de types ulcératifs qui sont divisés en lésions caséo-ulcératives (stade avancé de type caséo-nodulaire) et le type de lésions fibreuses, qui s'étend de la cavité à parois minces, kystiques ou modérément épaisses, aux cavités à parois fibreuses épaisses. Le groupe 6 comprenait un type bronchiectasique pur, qui ne put être distingué en apparence d'aucune autre bronchiectasie, mais qui se montra être du à l'histoplasmosis capsulatum. Le groupe 7 était un type pleural consécutif à l'infection de la plèvre par l'histoplasmosis capsulatum; un huitième groupe fut un composé de deux ou plusieurs des autres types.

En préparant les examens de ce matériel d'étude, une étude exhaustive fut faite sur les nombreux types d'artéfacts qui furent éliminés ou identifiés par des colorants spéciaux lorsque ce fut possible.

Le colorant jugé le meilleur pour mettre en évidence la mycose fut l'argent méthénamine de Gomori (G.M.S.) adapté par Grocott à cette recherche.

Sur 16 cas actifs incontestablement positifs, 14 furent mis en cultures et/ou inoculés aux souris, mais 7 seulement se révélèrent positifs.

Les constatations furent confirmées lorsque c'était possible par l'usage du polariscope, comme le recommandent Potenza et Feo. S'il ne fait pas le diagnostic, il aide à montrer la présence d'une substance polarisante, probablement un polysaccharide.

L'auteur propose une théorie sur l'évolution possible des parasites dans le corps humain, évoluant depuis les cellules phagocytées par les macrophages jusqu'à une forme sporulée quiescente dans le tissu fibreux, avec plus tard le réveil de ces spores (endospores) qui se transforment en levures actives après un temps variant de mois et d'années jusqu'à des décades.

L'étude ultérieure de ces possibilités sera reprise dans un travail futur où une discussion plus étendue sera possible.

ZUSAMMENFASSUNG

Es wurde eine vorläufiger Bericht zusammengestellt über die pathologischen Befunde von nachgewisener Histoplasmose in 21 umschriebenen Herden und 16 klinisch aktiven Herden. Zusätzlich ergaben sich 3 zweifelhafte Fälle in jeder Gruppe, bei denen eine Histoplasmose angenommen wurde, ohne dass man typische Parasiten hätte finden können.

Es wurden 24 weitere Preparate untersucht, bei denen keine Histoplasmose gefunden wurde. Diese dienten als brauchbare Kontrollfälle, weil es sich hauptsächlich um Tuberkulose handelte, bei denen säurefeste Bazillen gefunden wurden, und 3 Fälle von Bronchuskarzinom. Sie wurden mit hinzu genommen in Anbetracht der grossen Ähnlichkeit der klinischen, röntgenologischen oder anderer Befunde mit der Histoplasmose.

4 klinisch aktive Fälle lagen vor, die sowohl säurefeste Bazillen, als auch H. capsulatum enthielten. Ausserdem wurden 3 Fälle von nachgewiesenem Sarkoid ebenso wie viele Kontrollfälle mit anderen Krankheiten gefärbt und untersucht, aber Parasiten wurden nicht gefunden.

Es lagen 2 Serien von Fällen vor, die eine umfasste scheinbar inaktive Erkrankungen mit sogenannten Rundherden, und die andere bestand aus klinisch aktiven Krankheitsfällen.

Folgendes waren die pathologischen Befunde: Gruppe I mit zentrifugal geformten sphärischen Herden; Gruppe II mit verkapselten Infiltraten; Gruppe III mit käsigen knotigen Herden, ähnlich wie käsige Tuberkeln im Durchmesser von 1—15 mm sowie fibrokaseöse kalkhaltige und kalkig ossifizierte Herde; die IV. Gruppe bestand aus chronischen Pneumonien, und es wurde für richtig gehalten, sie zu unterteilen in verschiedenen Phasen ihrer zeitlichen Entwicklung von der histiozytären Infiltration und frühzeitig sich organisierenden Pneumonie mit Histiozyten bis zu den späten granulomatösen Herdformen, die ein Sarkoid vortäuschen; Gruppe V war der ulzeröse Typ mit Unterteilung in käsig-geschwürige (ein weiter entwickeltes Stadium der käsig-knotigen) und den fibrösen Typ von Herden. Letzterer reichte von dünnwandigen zystischen, über mässig dickwandige zu fibrös-dickwandige Kavernen. Die VI. Gruppe bestand nur aus Bronchiektasen, die im Aussehen nicht unterschieden werden können irgendwelchen anderen Bronchiaktasen, von denen sich aber heraus stellte, dass sie die Folge einer Infektion mit H. capsulatum waren. Gruppe VII war der pleuritische Typ, der die Folge der Invasion der Pleura mit H. capsulatum ist. Eine VIII. Gruppe war eine Zusammensetzung von 2 oder mehreren der anderen.

Bei der Vorbereitung zur Prüfung dieses Materials wurde eine erschöpfende Studie angestellt über viele Typen von Artefakten; sie wurden entfernt oder identifiziert mittels Spezialfärbung, so oft es ging.

Als die beste Farbe zur Färbung von Sprossenpilzkörpern erwies sich die Gomori-Methenamin-Silber Farbe (G.M.S.), die von Grocott als für die Identifizierung geeignet angegeben wurde.

Von den 16 endgültig positiven aktiven Fällen wurden 14 kulturell verarbeitet und/oder an Mäuse verimpft, jedoch nur mit 7 positiven Ergebnissen.

Die Befunde wurden, wo es möglich war, bestätigt durch die Verwendung des Polariskops nach der Empfehlung von Potenza und Feo. Wenn auch nicht von diagnostischem Wert, zeigt es doch die Anwesenheit einer polarisierenden Substanz, wahrscheinlich eines Polysaccharids.

Eine Theorie wurde entworfen hinsichtlich der möglichen Entwicklung der Parasiten im Körper aus den phagozytierten Zellen in den Makrophagen zu einer ruhenden sporenartigen Form im Bindegewebe mit späterer Reaktivierung dieser sporenartigen Formen (Endosporen) zu aktiven Sprossenpilz-Zellformen während eines Zeitraumes, der schwankte zwischen Monaten, Jahren und Jahrzehnten.

Eine weitere Ausarbeitung dieser Möglichkeiten wird in einer folgenden Arbeit ausgeführt werden, in der auch eine grössere Diskussion möglich ist.

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Bronchial Photography with Simple Apparatus in Sanatoria*

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Interest in bronchial photography centers mainly around two aims: visual material is obtained for consultation and for teaching, and permanent records of clinically interesting cases are made for further reference and follow-up. The pioneer work has been done in America by Holinger[1]; in Europe Soulas[2] and the French school have contributed much to start this field. In these large centers most of the recording is made with a film camera. This gives the advantage of also observing the motion but increases the cost of the apparatus, so that it cannot be acquired by smaller institutions.

For purposes of case studies in a sanatorium it is sufficient to be able to make still pictures of the observed lesions in the bronchial tree. This enables the whole staff to see the extent and location of the bronchial changes, which otherwise are only seen by the bronchologist through the tube and telescopes.

Two recent techniques of bronchial photography have been described, both of which are based on the same idea: the illumination is led via a quartz rod into the tip of the bronchoscope. The apparatus by Dubois de Montrenayd[3] employs a 6 V. proximal auto lamp as a source of continuous light, which makes also bronchial films possible. The apparatus is now becoming commercially available, but its total price would still be a considerable burden on the economy of smaller clinics.

Another apparatus, commercially available for a short time (manufactured by the Storz Company), employs an electronic flash as a proximal light source. Because of this, only momentary pictures can be taken. The price of the apparatus is in reasonable limits and nearly all institutions interested in bronchial photography are in a position to purchase it. Experience with this equipment will be reported here.

Apparatus and Technique

Bronchoscope. The tube is of elliptical diameter with 8x10 mm outsurface diameters. The distal end of the tube is somewhat broader than usual, and it is often necessary to turn the tube 90 degrees to the side when passing the vocal cords. Otherwise the broad tip may be difficult to introduce without traumatizing the epithelium of the cords.

Telescopes. These can be obtained with straight angle, 45 degrees, and straightforward vision. Each telescope accommodates a quartz rod running parallel to the viewing tube proper. It is necessary to give oxygen through the bronchoscope during photography as the telescopes occupy most of the tube space. A flow of 8 to 10 liters/min. is enough to allow the patient sufficient oxygen when the pictures are made.

*From the Satakunta Sanatorium.

The greatest trouble in securing good pictures is to keep the moisture out of the lenses. I have found it best to keep the tips of the telescopes in a folded electrical heat-bag before they are used for photography. The temperature of the bag is not too hot for the bronchi as the telescopes do not contact the mucous membranes and there is enough time for making bright pictures before cooling causes blurring of the lenses with moisture.

Illumination. An electrical flash bulb is housed in each telescope and receives the current from a transformer; the length of the flash is less than 1/50 sec. A picture can be taken every 2 or 3 seconds. In the meantime the transformer is not ready to give the bulb another current stroke.

Camera. A Robot Star camera with a well fitting tip for the proximal end of the telescope is used. The automatic film shifting mechanism enables the whole series of pictures in one patient to be taken successively without rewinding the mechanism. The camera has a separate eye piece for the examiner who is able to see all the time while pictures are being taken. This contributes greatly to the success of the pictures since the exact location of the telescope and an unblurred view can be maintained.

The brightness provided by the flash is sufficient for Ectachrom film, but also black and white film can be used if prints are desired. The prints can be added to the patient's records, enlarged from the original 1 cm diameter negative. The color slides can be stored with detailed notes of the pictures and examined with a projector.

Dubois de Montrenayd[3] reports that in their clinic a film strip is made of the bronchi at every bronchoscopy regardless of whether the findings are normal or pathological. While realizing that this practice would be ideal for any follow-up study, I have made still pictures of the findings only if there have been evident gross changes in the bronchi. Generally I examine the bronchial tree first with ordinary telescopes and at this stage determine the areas to be photographed. The straight-vision photographic telescope is always used first because it employs the distal light of the bronchoscope itself. For the upper lobes, the straight angle photographic telescope is introduced. The structure of the apparatus necessitates switching off the distal bronchoscope light in order to furnish the telescope with illumination. After the upper lobe pictures are taken, the telescope is withdrawn and the bronchoscope light reconnected.

After the desired photographs have been taken the bronchographic procedure, employed routinely in combination with bronchoscopy, is made by a method previously described.[4] The tube is withdrawn, the patient is wheeled to the roentgen department and bronchograms are made.

Results and Comment

It has been pointed out earlier[4,5] that to limit the examination of the bronchial tree only to the major bronchi, as is done in bronchoscopy, leads to an incomplete and sometimes erroneous conclusion regarding the condition of the bronchi. There are, of course, numerous cases where the pathological changes are localized in the area visualized in bronchoscopy, but there are also many others in which the changes seen in bronchoscopy

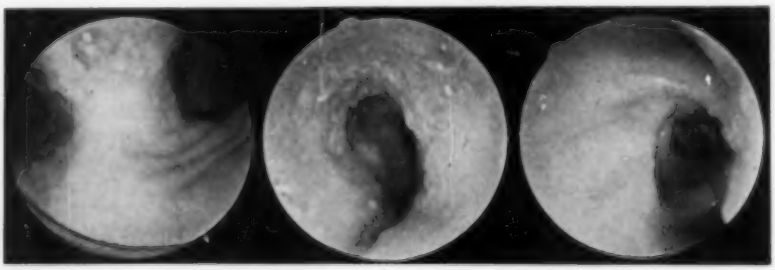
are only minor reflections of much greater pathology beyond vision. For a more definite judgment of the therapeutic measures needed for each individual patient, it is therefore often necessary to map the medium-sized and smaller bronchi with contrast medium. The typical photographic findings are therefore in some cases discussed together with the information obtained from the bronchograms.

The carina is the first landmark whose appearance often shows deviations from the normal. In figure 1A a normal carina is seen with thin mucous membranes and clearly defined intercartilaginous depressions. In figure 1B the carina is distorted owing to a scirrhous right upper lobe process; on the right in figure 1 there is a flattened carina with an open fistula (arrow) leading to a tuberculous glandular involvement under the carina.

Carcinoma of the bronchus (Fig. 2), if readily visualized, generally does not need an additional bronchogram. In our experience photographs of the involved area are of great help as the extent of the lesion can be exactly seen and studied at leisure by the whole staff in consultation with the thoracic surgeon. In Fig. 2 the epidermoid carcinoma involves the carina (2A), occludes a large part of the right main bronchus (2B), and extends on the lateral wall beyond the orifice of the middle lobe bronchus (2C).

A B C

FIGURE 1: A. Normal carina. B. Distorted carina. C. Carina with an open fistula.



A B C

FIGURE 2: Bronchial carcinoma. A. Infiltration of carina. B. Carcinomatous growth in the whole right main bronchus. C. Infiltration of the lateral wall at the level of the middle lobe orifice.

Bronchiectasis is not often definitely diagnosed bronchoscopically, especially if the patient has already expectorated the mucus out of the bronchi. Figure 3 depicts a case of this kind where the right side shows nearly normal middle and lower lobe bronchi (Figs. 3A and 3B). The bronchogram, however, shows clear cylindrical and saccular bronchiectasis both in the middle lobe and in the basal lower lobe segments (Fig. 3C).

On the same patient the diagnosis of bronchiectasis could be made definitely, even before the bronchogram, from the abundance of the secretions on the left side. Figures 4A and 4B show views before and after suction at the level of the three basal segmental bronchi. The bronchogram discloses that all three branches of the left lower lobe are involved with saccular bronchiectasis (Fig. 4G).

Tuberculous changes in the bronchi can be seen in Figures 5 to 7. Pure inflammatory tuberculous processes without stenoses or granulations are best seen in the original ectachromes as the conversion into black and white fails to show most of the details of the epithelial surface. Figure 5A shows a process in the right upper lobe: the mucous membrane is thick and edematous. The narrow orifice of the posterior segment is clearly visible but the others are covered with yellow pus extruding from the narrow apical opening. The bronchogram of this patient (Fig. 5B) shows a rather

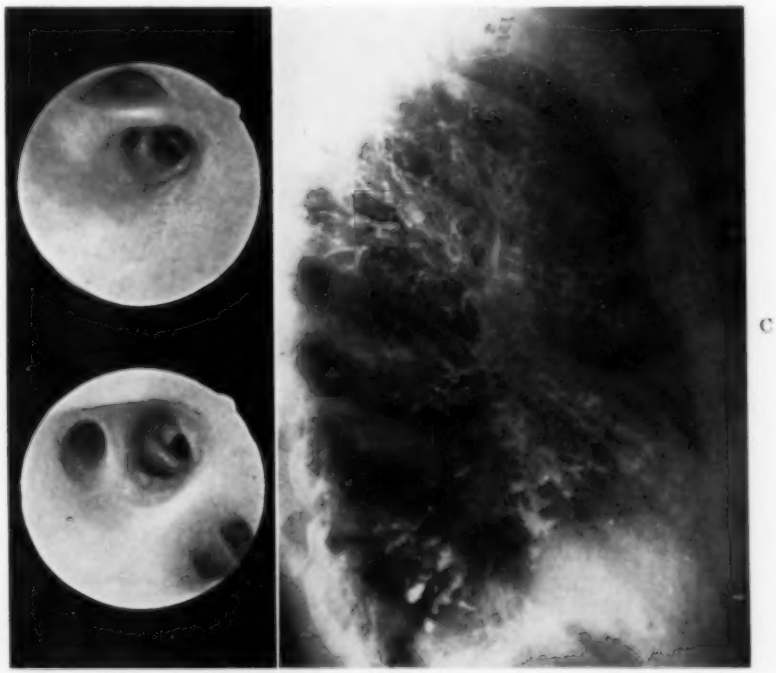


FIGURE 3: Bronchiectasis. A. Middle lobe and entrance to the lower lobe. B. Lower lobe orifices. C. Lateral projection bronchogram with bronchiectasis in the middle lobe and basal lower lobe segments.

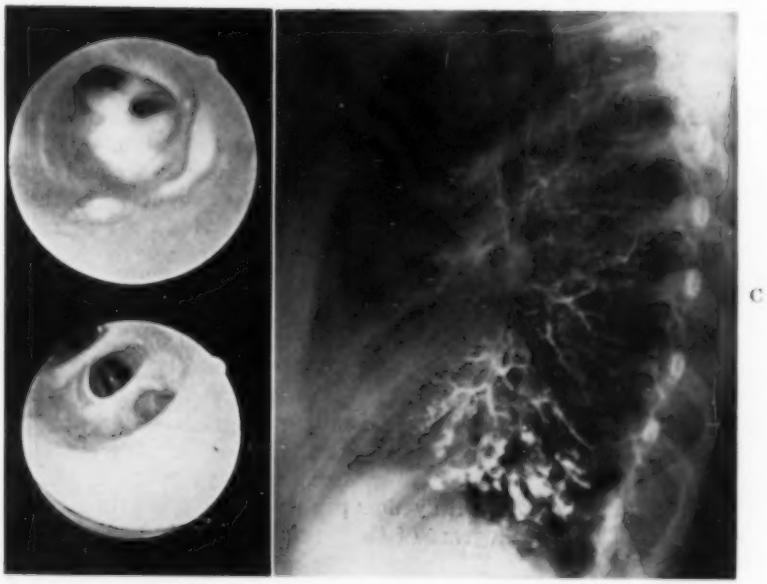


FIGURE 4: Bronchiectasis. A. Left lower lobe before suction. B. The three basal segmental orifices after suction. C. Lateral projection bronchogram with bronchiectasis in the basal lower lobe segments.

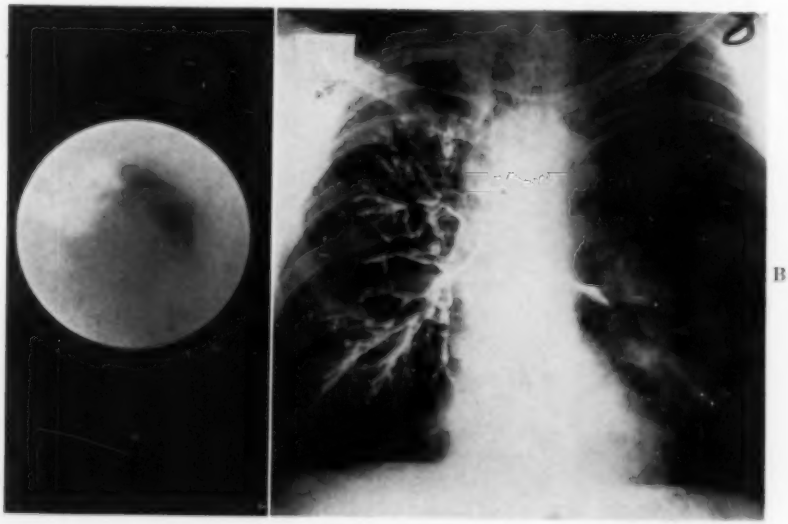


FIGURE 5: Tuberculous endobronchitis and bronchiectasis. A. Active inflammatory process in the right upper lobe. B. A-P projection bronchogram with bronchiectasis in the apical and posterior segmental bronchi.

narrow branching for the three segmental bronchi of which especially the apical and posterior division are ectatic.

Figure 6 shows a case with old, inactive stenosis at the level of the right middle lobe bronchus. Only a narrow rim of the middle lobe bronchus is seen while a tense, fibrous scar surrounds the medial part of the middle

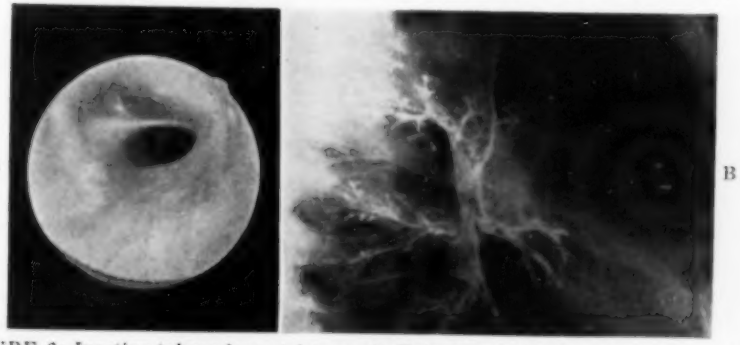


FIGURE 6: Inactive tuberculous stricture. A. Entrance to the right lower lobe; above it a narrow orifice to the middle lobe. Healed scar tissue surrounds both orifices at the medial wall. B. Lateral projection bronchogram with narrowed lumina at the junction of the middle and lower lobe bronchi.

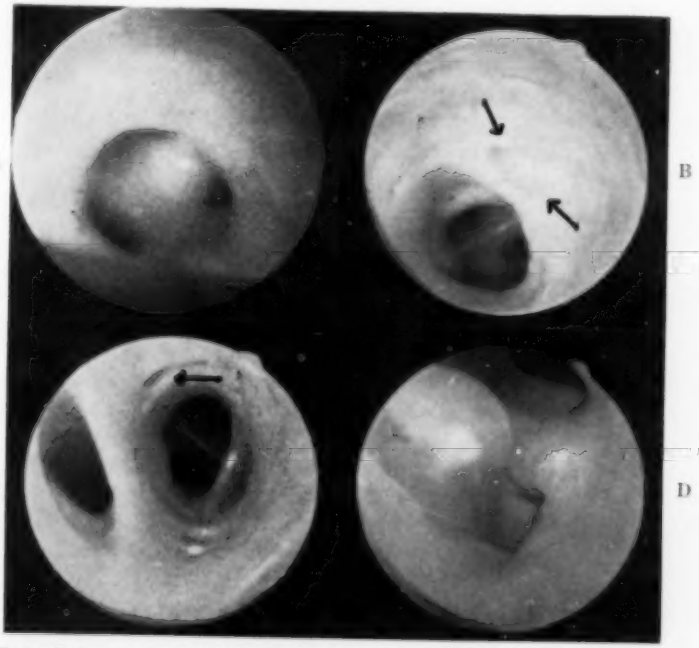


FIGURE 7: Tuberculous endobronchitis. A. Inactive, right upper lobe process with narrow orifices and thick intersegmental septa. B. Healed scar in the medial wall of the left lower lobe bronchus. C. Open fistula at the level of the mediobasal segment of the right lower lobe bronchus. D. Occlusion of right lower lobe bronchus with tuberculous granulomatous lesion.

and lower lobe entrance (Fig. 6A). In the bronchogram (Fig. 6B) this scarry branching is evident. However, it is worth noticing that middle lobe bronchi fill well in spite of the deformed anatomy.

Further tuberculous changes are shown in Figure 7. Figure 7A shows a right upper lobe orifice with very thick intersegmental septa but with non-active mucous membrane. In Fig. 7B an old scar, resulting from a healed fistular process, is seen in front of the basal segments of the lower lobe bronchus (arrows). Figure 7C shows an open fistula (arrow) in the right lower lobe bronchus as the level of the mediobasal segment. Finally, in Fig. 7D, an active, stenosing, granulomatous occlusion of the lower lobe bronchus is seen in the right bronchus at the level of the middle lobe orifice.

Bronchial photography gives in many cases valuable data for case conferences in a sanatorium and makes the pathological bronchial changes, described by the bronchologist, clearer and more meaningful to the phthisiologist. Together with the bronchogram, and with analyses of the bronchial secretions,[6] bronchial photography helps to clarify the condition of the bronchial tree.

SUMMARY

Experience with bronchial photography in a sanatorium is reported. The apparatus is simple and not expensive; only still pictures can be made. Typical gross changes in the bronchi are described. Photographs of the lesions are valuable in staff conferences, consultations, follow-up studies, and in teaching.

RESUMEN

Se informa de la experiencia con la fotografía bronquial en un sanatorio. El aparato es sencillo y no costoso; sólo se toman vistas fijas. Se describen las alteraciones gruesas típicas en los bronquios. Estas fotografías son valiosas para las conferencias del personal médico, consultas, seguimiento de enfermos y para la enseñanza.

ZUSAMMENFASSUNG

Bericht über Erfahrungen mit bronchialer Fotografie in einem Sanatorium. Die Apparatur ist einfach und nicht kostspielig; es können nur unbewegliche Bilder gemacht werden. Typische makroskopische Veränderungen in den Bronchien werden beschrieben. Fotografien der Herdbildungen sind von Wert bei Konsilien, Konsultationen, Verlaufsbeobachtungen und für den Unterricht.

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Abeyant Tuberculosis*

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Abeyant tuberculosis is a state of armed neutrality between the host, man and the tubercle bacillus. In particular, it is a prognosticative as well as descriptive label for those individuals with evidence of past tuberculous infection, and no evident clinical disease. It describes the group that produces much of the communities' active, infectious cases of tuberculosis.

The importance of abeyant tuberculosis became manifest during 1952-53 in the course of an evaluation of the tuberculosis control program in Polk County, Iowa.[1] A study of the median ages in relation to the stage of reported disease showed: minimal, about 30 years; moderately advanced, about 45 years; and far advanced, about 55 years. Among those who sought medical attention because of symptoms, there were slightly more women than men in the moderately advanced group; while among those with advanced disease, there were almost four times as many men as women.

It was found that 52 (63 per cent) of the 83 new cases of tuberculosis reported during the two year period came to the doctor because of symptoms of actual illness. In addition, a serious time lag between first suspicion of illness to final diagnoses became evident. Although 22 (27 per cent) were diagnosed within three months, the median time between onset of symptoms and diagnoses was over six months. Of the total group, 19 (23 per cent) had a delay of more than one year. The inescapable conclusion was that in a low incidence area, there was need for a re-evaluation of case finding and educational methods and techniques based upon the facts as ascertained as well as the changing character of the disease itself.

First, it must be acknowledged that active tuberculous disease is frequently difficult to diagnose; that physicians hesitate to treat anyone upon initial suggestive physical and/or x-ray evidence alone in the absence of positive laboratory findings, and rightly so.

Second, the great majority of clinically active tuberculous disease results from a recrudescence of previously abeyant infection. We must remember that the morbid picture of only a few decades ago when large numbers of young persons developed tuberculous pneumonias or extensive, rapidly progressive disease was the host-parasite relationship in the environmental and medical care setting of that period. Now, the problem

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focuses primarily upon men over 40. Clinically active tuberculosis is no longer predominantly a disease of youth.

Third, our communities have been lulled by the huzzas of the professions over the dramatic, continuing decline in the tuberculosis mortality rates, in spite of the distressingly slower decline in morbidity rates.

Fourth, x-ray screening surveys do not detect the individuals who have been infected, and do not present evidence of active pulmonary disease. These are individuals who were temporarily victorious in their first encounter with tubercle bacilli.

These overlooked individuals have abeyant tuberculosis. They constitute the group of people that in the past have been given to believe that they had healed themselves. When this belief is coupled with the fact that people's attitudes toward both tuberculosis and detection programs are still frequently colored by fear and/or misunderstanding, the usual x-ray survey programs are foredestined to only partial fulfillment of function.

A recent inquiry in three high incidence areas as to why people obtain x-ray films showed that those who believed they might get tuberculosis, those who do not rely solely on symptoms as a stimulus for seeking a chest x-ray film, and those who see benefits to themselves in early detection are likely to obtain x-ray films voluntarily regardless of economic status, sex, or age. (2) What became evident however, was that what people do or do not do is not a function of information. Action results from a real belief and a conviction that such information applies to them personally and that it is important to them as individuals. Education, or information in itself is neither motivation nor action.

All these factors are the basis of a pilot study initiated in Polk County during 1956, a program to bring under Health Department surveillance those individuals with evidence of past tuberculosis infection, and no clinical disease. This was centered for Polk County in the local health department, and co-ordinated with the State and County Tuberculosis & Health Associations, our health professions, schools, multitude of interested community groups and agencies, as well as U.S. Public Health Service, and the State Health Department. It is supported as a research project by the Iowa Tuberculosis and Health Association.

A companion follow-up file to the usual tuberculosis registry was created for those with abeyant tuberculosis. The card, specially designed for this investigation is in a section of the tuberculosis case registry file. The abeyant file will be fed from several sources; the tuberculin testing programs in schools; contacts to cases of active disease, private physicians, as well as the county-wide miniature x-ray filming service. Those with suggestive x-ray evidence of past tuberculosis infection will be tuberculin tested for verification. The importance of the tuberculin test as either a necessary adjunct to x-ray film surveys or as a screening procedure is manifest.

Children with positive tuberculin reactions will be placed in the Abeyant File upon reaching the age of 15, as well as act as the reason for testing their adult contacts. With the recent extension of the local x-ray film

program to the community groups with the highest morbidity, jail, transient and elderly populations, it will be possible to separate out those individuals who must be followed and from whom we can expect the active tuberculosis of the tomorrow. It is of interest that this program during 1956 produced two cases of active tuberculosis from 88 transients x-rayed, three cases in 405 persons in our city and county jails, and none in the 865 elderly individuals from Golden Age Clubs and nursing homes. The first two groups produced one active case of tuberculous disease per 100 films. In addition, there were 26 individuals with findings suspect of tuberculosis; the old age group produced but seven such persons. It would have been these individuals who would spread the disease to their families and community, unknowingly, and for many months; if not uncovered and kept under surveillance.

Since its initiation, the file is accumulating slowly. It was planned to start cautiously. The committee responsible for this program has clarified the study and its import to date by concluding:

1. Only those with a positive tuberculin reaction will be in the Abeyant File, irrespective of original method of referral.
2. Those groups with the highest incidence of disease require added Health Department and Tuberculosis Associations' efforts.
3. Education material, pertinent to the goal of the program will be sent to those placed in the abeyant file along with the predetermined periodic reminders to have a chest x-ray film.
4. An indication of intention will be sent whereby public health nurses can concentrate on those who do not intend to follow through on their own accord.
5. A routine of notification will permit follow-up of those who will not have availed themselves of x-ray services.
6. An acknowledgment that the project has several values; case findings, case holding, health education and research, with an opportunity to evaluate each facet.

Of special importance is the opportunity to study the methods and techniques necessary and peculiar to motivating people with Abeyant Tuberculosis. A person must know what to do, when to do it and how to do it before he can take action. But merely knowing these things is insufficient in itself to elicit the action to which they relate. There must be motivation. The least desirable is passive acceptance of easily available x-ray screening services brought to people with the added prompting through exhortation and veiled dire prophecies. The ultimate is for informed people to do that for themselves which they know they should do for themselves.

It is hoped that with careful and meticulous study and evaluation it can be determined how best to progress toward the goal of developing the individual's sense of responsibility for his own health as well as fulfill our responsibilities in tuberculosis control of uncovering as well as preventing tuberculous disease and its spread through our community.

SUMMARY

A pilot study was initiated to follow by means of periodic reminders as well as follow-up visits by nurses of the Des Moines-Polk County Health Departments of all individuals with abeyant tuberculosis (tuberculin reaction but no evident clinical disease) brought to the attention of the health department from x-ray or tuberculin surveys.

This group with evidence of past tuberculous infection is considered to produce much of the community's active tuberculosis. Re-evaluation in the county had emphasized this fact.

The preliminary study will permit evaluation of case finding, case holding, and health education as it pertains to those previously ignored individuals in whom there is a state of armed neutrality between the host and tubercle bacillus.

RESUMEN

Se inició un estudio piloto para observar a los individuos infección tuberculosa (con reacción tuberculínica, pero sin evidencia clínica), se ha emprendido por medio de recordatorios periódicos así como por visitas de observación por enfermeras del Departamento de Salubridad del Condado de Polk en Desmoines. Estos infectados fueron descubiertos por el departamento de Salubridad por los rayos á o por investigaciones tuberculínicas.

Este grupo con evidencia de infección tuberculosa anterior se considera que produce mucha de la tuberculosis activa en la comunidad.

La revalorización en el condado ha destacado este hecho.

El estudio preliminar permitirá estimar la búsqueda de casos, el control de los casos, y la educación higiénica como corresponde a estos individuos antes ignorados en quienes hay un estado de neutralidad armada entre el huésped y el bacilo.

RESUME

Une étude-pilote fut entreprise pour suivre au moyen de rappels périodiques aussi bien que de visites systématiques par des infirmières des Services de Santé du "Des Moines-Polk County Health Departments" tous les individus ayant une tuberculose stabilisée (réaction tuberculinique positive, mais sans atteinte clinique évidente) signalée à l'attention du service de santé par des contrôles radiologiques ou tuberculiniques.

Ce groupe de malades, porteurs d'une infection tuberculeuse ancienne évidente, est considéré comme produisant le grand nombre des tuberculoses actives de la collectivité. Une nouvelle estimation dans la région a mis ce fait en évidence.

L'étude préliminaire permettra d'évaluer l'importance du dépistage, du traitement, et de l'éducation sanitaire, puisqu'elle s'adresse à des individus antérieurement ignorés chez lesquels il existe un état de neutralité armée entre l'hôte et le bacille tuberculeux.

ZUSAMMENFASSUNG

Eine wegweisende Untersuchung wurde begonnen, um sowohl mit Hilfe periodischer Erinnerungsschreiben als auch mit Verlaufsbeobachtungsbesuchen von Pflegerinnen der Gesundheitsämter des Kreises Des Moines-Polk das Schicksal aller Induviduen zu verfolgen mit unentschiedener Tuberkulose (positiver Tuberkulinreaktion, aber keine klinisch augenscheinliche Erkrankung), wie sie zur Kenntnis des Gesundheitsamtes durch Röntgen- oder Tuberkulin-Reihenuntersuchungen gelangt war. Von diesem Personenkreis mit Anhaltspunkten einer vorausgegangenen tuberkulösen Infektion wird angenommen, dass er viel beiträgt zu den kommunalen aktiven Tuberkulosen. Eine Zeitberechnung im Kreis hat diese Tatsache unterstrichen.

Die vorläufige Untersuchung wird eine abschätzung der Fallsuche, des Fallbestandes und der Gesundheitserziehung ermöglichen, wie sie solchen zuvor übersehenen Personen zukommt, bei denen ein Zustand bewaffneter Neutralität besteht zwischen dem Wirt und dem Tuberkelbazillus.

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Bronchoscopic Criteria for the Diagnosis of Tuberculous Lymph Node Perforation into the Bronchial Tree of the Adult

A Critical Analysis of 700 Cases

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Perforation of caseous lymph nodes into the bronchial tree is of relatively frequent occurrence in the course of tuberculosis in children. The importance of this complication in the pathogenesis of the disease as well as in certain clinical and roentgenological findings is well understood by clinicians and pathologists. It has also been known for many years that in elderly people anthracotic or caseous lymph nodes may occasionally break through into bronchi or into mediastinal structures, sometimes causing serious clinical manifestations. With the introduction of large-scale bronchoscopy, lymph node perforations were also observed in adolescents and young adults suffering from pulmonary tuberculosis especially in the primary or post-primary phase of the disease,[1] but according to most observers active tuberculous processes of pulmonary lymph nodes are of no great practical importance in the adult type of pulmonary tuberculosis.

Pathologists like Schwartz[2,3,4] and Uhlinger[5] oppose this generally accepted view. On careful systematic investigations on autopsy material of more than 700 cases Schwartz observed in a large proportion of cases lymph node penetrations into the airways of adults suffering from pulmonary tuberculosis in all stages. In his opinion, periodic re-activation and perforation of caseous pulmonary lymph nodes are responsible in most cases for endogenous re-infection and for the spread of the process in chronic pulmonary tuberculosis of the adult.

Some recent bronchoscopic observations seem to support the theory of Schwartz. In a number of publications from various clinics, bronchoscopists recorded perforations or residues of perforations with great frequency in adult patients. Lévi-Valensi, Zaffran and Morena[6] describe 25 bronchial fistulae in Algerian patients 18 to 61 years of age. Vaksvik,[7] on bronchoscopic examination of 1003 adult patients in Norway, found 134 cases with perforations or residues of perforations. Iselin and Suter[8] and Meng[9] report similar numbers from Switzerland: 131 perforations or scars in 1370 consecutive bronchoscopies. Tricoire[10] in France observed 16 cases of lymph node perforation in adults and quoted a publication of Chatonnier and Zaffran[11] who found 37 fistulae in 120 adult patients. Most recently,

*This article is based on our experience in the Department of Medicine, Surgery and Pathology, in the Malben Beer Yaacov Hospital for Chest Diseases, services of the American Joint Distribution Committee in Israel, which receives its budget from the United Jewish Appeal.

Popper c. s.[12] reported their experiences in 1257 patients, 950 of whom suffered from pulmonary tuberculosis. In 117 cases they found perforations of lymph nodes or bronchial fistulae (109 in the tuberculous group and eight in the non-tuberculous group).

The bronchial findings described by various authors may be grouped in pathognomonic and suggestive signs. Pathognomonic signs of lymph node perforation are broad irregular funnel-shaped openings in the bronchial wall, surrounded by, and partially filled with coarse granulation tissue. In the fistulous tracts caseous or anthracotic material from the lymph nodes is visible. Another characteristic picture is a furuncle-like elevation of the mucosa with central umbilication. In most cases, it is possible to expel by pressure with the bronchoscope some purulent material which usually contains tubercle bacilli. On repeated bronchoscopies one can observe that healing takes place by scar formation.

As suggestive signs of lymph node perforation other bronchoscopic pictures were described, e.g. round circumscribed openings in the mucosa, small ducts or as punched-out holes. The diameter of these mucosal holes varies from pin-point size to 2 to 3 mm. Frequently, the lumen widens during inspiration. The mucosa covering the holes is usually of normal appearance but at times may show signs of inflammation. Not infrequently mucous and even purulent secretion is observed and, in rare cases, smooth translucent granulation tissue is found in the wall or in the depth of the holes. The French authors emphasize that the appearance of these openings does not change on repeated bronchoscopic examinations.

Indirect signs of former lymph node penetration are described as mucosal scars—especially funnel-shaped or starlike retractions—humps or callous prominencies, local discoloration of the mucosa or isolated patches of anthracotic pigmentation. According to many authors, these findings make a diagnosis of a former perforation likely, particularly if they appear in combination with certain clinical symptoms and roentgenologic patterns. Vaksvik is of the opinion that most cases of bronchostenosis, ulceration or local proliferation of granulation tissue are caused by perforation of tuberculous lymph nodes.

Analysis of Our Material

In an attempt to re-examine the theory of Schwartz and to re-evaluate the bronchoscopic findings of the above mentioned authors we made a survey of 700 consecutive patients who had undergone bronchoscopic examinations during the years 1951-1954.

At the Beer Yaacov Chest Hospital bronchoscopic examinations are performed on every patient in whom clinical symptoms or roentgenologic signs point to an involvement of the lymph nodes or of the bronchi and, furthermore, in every case that requires decision about possible operative intervention. At every examination, the bronchial tree including the orifices of the segmental bronchi is carefully inspected with telescopes.

Table I gives a summary of the most important lesions found. We adopted the terminology of Vaksvik in order to be able to compare our findings with

TABLE I

Bronchoscopic findings at:	Glittre San. 1946 - 1952		Beer Yaacov Hospital 1951 - 1954	
Number of patients	1,003		700	
Number of bronchoscopies	1,262		916	
Definite lymph node perforation	20	(2%)	....	
Suspected lymph node perforation	....		7	(8%)
Mucosal holes	81	(8%)	49	
Mucosal scars	33		8	
Stenosis	53		41	
Granulations	23		8	
Ulcerations	9		8	
"Cushions"	12		1	

those at Glittre Sanatorium. The above table shows that we also found pathological changes in the bronchial wall in a great number of our patients. For reasons which will be discussed later we do not accept many of the so-called indirect signs, described by other authors as characteristic for lymph node perforation and cases with such findings are not included in our analysis. We selected 64 cases for further study, 8 of whom showed star-shaped or funnel-shaped retractions and 56 presented holes in the bronchial mucosa.

With the exception of one boy of 16 all these 64 patients were adults, 18-57 years of age; the sex distribution was about equal. All were recent immigrants, more than one half of them from Europe, while the others hailed from Arabian countries or from North Africa.

Table II shows the number of bronchoscopies performed on individual patients. In half of our cases more than one examination was made. The time of observation was longer than six months in about one fourth of the cases. Especially, when perforations were suspected repeated bronchoscopies were performed up to several years following the initial examination.

TABLE II
NUMBER OF BRONCHOSCOPIES IN PATIENTS WITH SUSPECTED PERFORATIONS, MUCOSAL HOLES OR SCARS

Nr. of examinations	1x	2x	3x	4x	5x	6x	Total
Nr. of patients	32	19	7	1	4	1	64
Nr. of bronchoscopies	32	38	21	4	20	6	121

Interval between bronchoscopic observations:

	Mucosal Holes Mucosal Scars	Suspected Perforations
3 - 6 months	16	1
7 - 12 months	5	2
13 - 24 months	3	2
25 - 36 months	1	2

In the eight cases with distinct mucosal scars, we compared the bronchoscopic findings with the tomographic pictures: All of them suffered from chronic phthisic form of tuberculosis and the mucosal scars were situated at the orifice of the bronchus leading to the main lesion. In five cases, a calcified lymph node was found in close contact with the bronchial wall at the site of the scar, and in five the roentgenologic appearance was typical for obstructive or peribronchial lesions.

As mucosal holes we considered circumscribed openings in the mucosa or small ducts from pin-head size to a diameter of 2 to 3 mm. In more than one half of our cases only a single lesion was observed, in one third there were two holes, usually in the same bronchus. In other patients we found a varying number of pathologic openings in different places; in two cases more than 10 holes were seen. In a total of 49 patients 98 holes were encountered. As may be seen in Figure 1a, the sites of predilection were the orifices of the right and left upper lobe bronchi, especially the anterior and lower walls, and to a lesser extent, the medial walls of the right and left main bronchi just beneath the carina. The mucosa covering the holes appeared normal in most of our cases. Frequently we observed inspiratory widening of the openings. In seven patients the mucosa was reddened and swollen, whereas the surrounding bronchial mucosa was generally unaltered. Mucous secretion was noted 14 times and minimal purulent secretion was found four times oozing from the openings. In none of the cases was it possible to obtain sufficient material for a bacteriological examination. In five we saw smooth translucent grayish-red granulations at the bottom of the holes. Our observations correspond to those of other authors concerning number, localization and appearance.

We do not think that these findings by themselves are sufficient to make a diagnosis of lymph node perforation. We agree with Vaksvik that there are all sorts of transitional forms between active perforation, fistulous tracts and other pathologic openings in the bronchial tree.

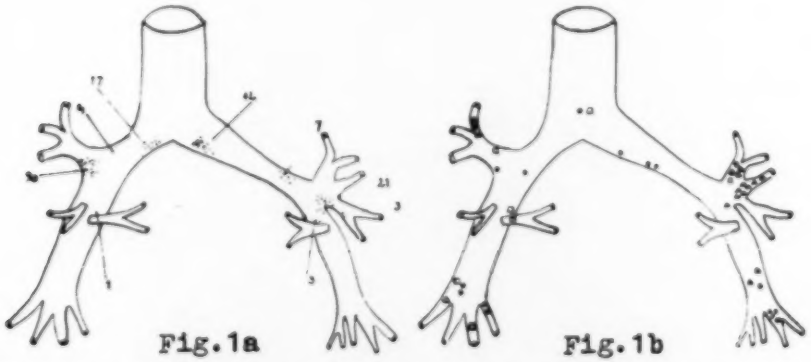

Figure 1a: Distribution of 98 mucosal holes in 49 cases.—*Figure 1b:* Localization of holes (°), crypts (Δ), and patches of anthracosis (□) in 15 post-mortem specimens of bronchial tree.

In the presence of larger openings the possibility of super-numerary or aberrant bronchi must be considered. Bronchographic and tomographic examination can classify the nature of such findings. The small holes, however, that were noted by us and by many authors quoted above* may represent fistulous tracts or pathologically enlarged ducts of the mucous glands.

The acini of the mucous glands are situated deep below the bronchial mucosa. A relatively long and narrow duct traverses the different layers of the bronchial wall in an oblique direction and widens before entering into the bronchial lumen. Under normal conditions the small openings cannot be visualized. Inflammatory processes involving the mucous glands or foreign material penetrating into the lumina of the ducts may cause abnormal dilatation. Inflammatory changes at the narrow neck of the ducts may cause local obstruction followed by cystic dilatation of the glands, accumulation of purulent secretion in these sacs and finally perforation into the bronchial lumen. Mechanical factors such as chronic cough possibly play also a part in the pathogenesis of these lesions.

It is possible to demonstrate the dilated ducts or cysts on bronchographic examination. They appear as small diverticuli or as isolated droplets. When there are multiple cysts the bronchial wall appears serrated or irregular. Huizinga[13] and after him other authors described the typical roentgenologic appearance especially in patients suffering from bronchitis or from bronchial asthma. Figure 2 shows the bronchographic picture of glandular cysts in one of our patients, in whom we found more than 10 mucosal holes on bronchoscopic examination.

Duprez and Mampuys[14] studied the topography of the mucosal glands and the occurrence of dilated glandular ducts by means of bronchial casts

*Compare e.g., the illustrations in the paper by Lévi Valensi c. s. Rev. de la Tuberc., 15:410, 1951 pp. 412-413.

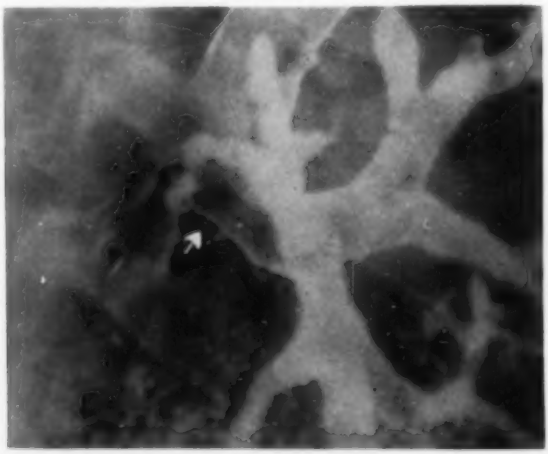

FIGURE 2: Bronchographic picture of mucosal holes.

and of special preparations of the bronchial mucosa. They found the pathologic changes most frequently in the larger bronchi around the bifurcations. The authors compared their anatomic findings with the bronchoscopic appearance of mucosal holes and they stress that in most cases differentiation between glandular ducts and small fistulous tracts from bronchial lymph node perforations is impossible on bronchoscopic observation alone. They believe that, not realizing these facts, many clinicians report too high a percentage of perforations.

In our material none of the cases with mucosal holes, seen at bronchoscopy were available for anatomic study. There was no death among the patients examined and in cases that underwent lobectomy or segmentectomy the holes, which had been visualized were situated always proximally to the surgical plane of resection.

We, therefore, had to look for other comparable material and examined the tracheobronchial trees from individuals who died from various diseases. The trachea, bronchi and both lungs were removed *in toto* from the body and the same examiner who had done the bronchoscopic examinations *in vivo* introduced the bronchoscope into these preparations and searched for holes. However, none was found. The trachea and the bronchi were, then, opened posteriorly by cutting them longitudinally with scissors and a thorough search for holes was made with the magnifying lens by both the bronchoscopist and the pathologist. In this manner, a number of such lesions were discovered in spite of the negative findings on previous bronchoscopic examination by the lack of respiratory movements and dilatation so that the tiny holes remained collapsed and were further reduced in

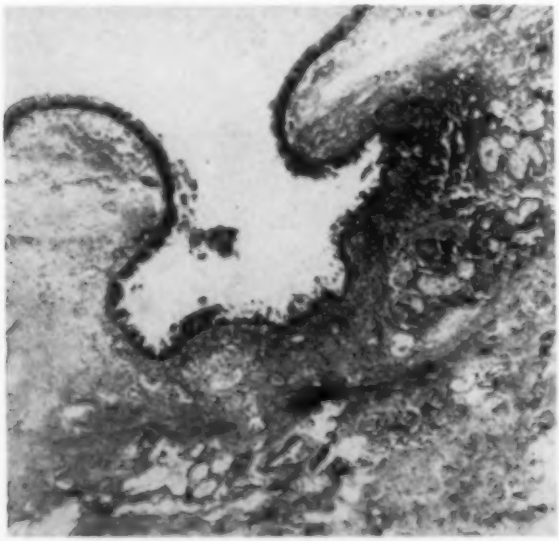

FIGURE 3: Flask-shaped duct with fibrosis and lymphocytic infiltration. Atrophy and cystic dilatation of bronchial glands.

size by the postmortem contraction of the bronchial muscles. The lesions were found lying singly or in groups at a location corresponding closely to that of the bronchial holes seen *in vivo* (Fig. 1b).

Fifteen specimens were examined in this fashion and in six of them typical holes were found grossly. In the other nine cases the bronchoscopist designated the openings seen as "crypts." These are considered as common findings—small shallow out pouchings or depression of the bronchial mucosa. The patients from whom these specimens had been taken varied in age from 37 to 82 years. Only one of them had advanced pulmonary tuberculosis and no hole was found in this case. Patients with positive findings died of a variety of causes, most of them unrelated to pulmonary disease. Five had signs of severe chronic bronchitis.

Histologic examinations were carried out on multiple blocks and some of them were sectioned in steps. Neighbouring sections were stained with hematoxylin-eosin and elastica-van Gieson. Basically a similar picture was found in all lesions examined and no clear-cut histologic differentiation was possible between so-called crypts and mucosal holes. The lesions represented either widened ducts of mucous glands, cone-shaped or flask-shaped, with narrow mouths, (Fig. 3) or globular depressions widely communicating with the bronchial lumen (Fig. 4). Inflammatory changes were present either in the depth of the ducts or at their necks. Some of the lesions showed no inflammatory changes. At times, the bronchial muscles were hypertrophic, forming a thick ring at the neck of a dilated duct. In the depth of the ducts and depressions, mucous glands were noted, some with mild chronic inflammatory infiltration, some without significant histologic changes and some with signs of mild atrophy.

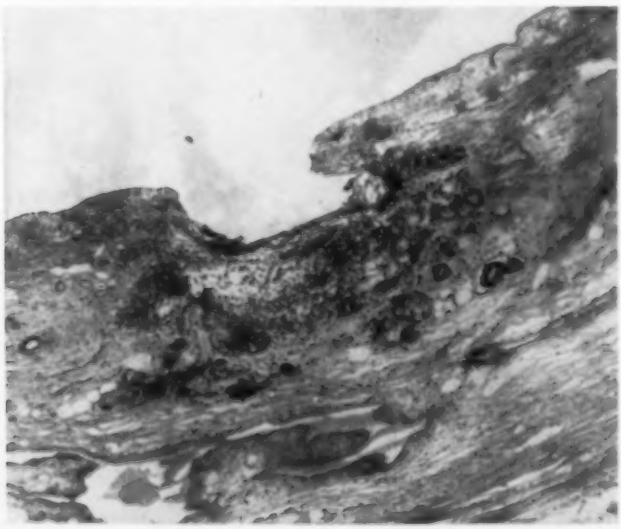

FIGURE 4: Crypt with wide neck. Inflammatory and other changes as in Figure 3.

In our limited material, we never saw association of these dilated ducts with disease of adjacent bronchial lymph nodes. At times, anthroco-silicotic or fibrotic lymph nodes were found attached to the bronchial walls in areas of ductal dilatation but from the histologic appearance this association was considered fortuitous.

These anatomic findings confirmed our opinion that most of the mucosal holes found were actually diseased excretory ducts. Other facts pointed in the same direction. Careful tomographic examination especially of the hilar region of our 49 patients failed to reveal enlargement of lymph nodes, nor were there pathognomonic clinical or roentgenologic signs of recent perforation. By far the greatest number of orifices noted were covered with normal mucosa and showed only mucous secretion. But also in cases showing signs of inflammation, purulent secretion or small translucent granulations, these changes were probably caused by an infection of the dilated ducts, since all these changes had disappeared on subsequent examinations. There remained, ultimately, only a hole covered by normal mucosa. The fact that the appearance of these openings did not change even after one or two years also seems to indicate that they were not due to bronchial fistulae.

In 22 patients the mucosal holes were situated in the bronchus leading toward the main lesion. It is true that lymph node perforation at this location may be responsible for the development of such a lesion; on the other hand mucous gland involvement may be caused by the regional parenchymatous process, so that this localization is not sufficient to differentiate the nature of the bronchial lesion.

Only in seven of our patients was a lymph node perforation suspected although none of them showed the pathognomonic bronchoscopic appearance. Holes were seen in all of them, some of which were more than 3 mm. in diameter, and nearly all showed signs of severe inflammation and purulent secretion for a long time. Where repeated control examinations were done, we observed that healing took place with scar formation. In addition, the clinical and/or roentgenologic findings suggested an active specific process of the hilar lymph nodes. Of these seven adults, one suffered from primary tuberculosis, in four others the pulmonary lesions were considered as direct sequelae of the primary infection (post-primary lesions) and only two patients suffered from a chronic phthisic form of tuberculosis. Appearance and development of the lesions is demonstrated by the following two typical cases:

Case 1: A 26 year old woman from Hungary was admitted following an acute episode of fever, cough and weight loss. X-ray film examination showed calcified lymph nodes between the right upper and middle lobes and confluent patchy lesions with a prune-shaped cavity in the postero-lateral segment of the right lower lobe. At the first bronchoscopy in January 1953, a hole was noted at the entrance of the right upper lobe bronchus, measuring 1 x 2 mm. in diameter, partially covered by granulation tissue. Control bronchoscopies at 3-month intervals disclosed a continuous diminution in the size of the hole with epithelization in its depth. In May 1954, only a funnel-shaped scar remained with dilated capillaries traversing the area. At this stage, a resection of the right lower lobe was performed. During operation, a group of enlarged soft lymph nodes was palpated around the bronchi of the middle and upper lobes.

Conclusion: In this patient a cavernous pulmonary process in the right lower lobe was probably a sequela of a bronchogenous dissemination from perforated lymph nodes. A residual perforation in the right upper lobe bronchus healed in the course of a year.

Case 2: On routine examination, a cavernous pulmonary process was discovered in a 30 year old man from Rumania. There were no clinical symptoms, but tubercle bacilli were found in the sputum on rare occasions. The roentgen picture, on admission, revealed widespread infiltrative and dense peribronchial changes in the apical and posterior segments of the right upper lobe. Calcified lymph nodes were noted close to the posterior wall of the right upper lobe bronchus. On bronchoscopic examination a crater-shaped opening, the size of a rice grain, was found on the medial wall of the right main bronchus 2 cms. below the carina. The floor of the defect was covered with purulent secretion. Under antimicrobial treatment, constant improvement of pulmonary and bronchial changes was noted. Five months following the first bronchoscopy, the floor of the defect was covered by smooth granulation tissue and the size of the opening diminished gradually. After 15 months, there was only a mucosal scar left with a central depression and capillary dilatation. The pulmonary process, at that time, was apparently arrested, the peribronchial changes had completely disappeared.

Conclusion: The bronchoscopic appearance was highly suggestive of hilar lymph node perforation. The pulmonary and peribronchial changes in the right upper lobe might have been related to the lymph node lesion. Both lesions healed concomitantly.

Discussion

In an analysis of 700 consecutive bronchoscopics on adults suffering from pulmonary tuberculosis we were unable to find a single case showing the pathognomonic picture of recent lymph node perforation into the bronchial lumen. However, we observed a great number of pathologic changes in the bronchial mucosa that could be classified as either suggestive or indirect signs of lymph node perforation. With regard to the latter there arises the question, if we are allowed to draw the conclusion that lesions like stenosis, granulations, superficial ulcerations or slight alterations in the appearance of the bronchial mucosa are invariably caused by perforation of a tuberculous lymph node, even in the presence of so called typical clinical and roentgenologic findings. The involvement of the bronchial tree by a tuberculous process may occur through various pathways: Extension of an inflammatory process from adjacent structures, direct implantation of contaminated material from the lumen, hematogenous and lymphogenous dissemination into the bronchial wall; lymph node perforation is only one of the possible pathogenic mechanisms.[15, 16] For these reasons we excluded 58 cases with stenosis, granulations, ulcerations or "cushions" from further analysis and we accepted only star-shaped or funnel-shaped retractions of the bronchial mucosa as possible remnants of a former lymph node perforation. We observed eight such cases in our series.

As for so-called suggestive signs of lymph node perforation, we collected 64 cases with abnormal openings in the bronchial mucosa, an incidence similar to that reported from other institutions, especially those that differentiate between definite perforations and mucosal holes, as e.g. Glittre Sanatorium (8 per cent).

In only seven of our patients we suspected perforations of a tuberculous lymph node into the bronchial wall.

The low incidence in our material may be due in part to a different patient population. Most of our patients were new immigrants, adults with chronic pulmonary tuberculosis of long standing. In institutions, where more adolescents are admitted, suffering from the primary or post-primary phase of tuberculosis typical lymph node perforations will undoubtedly be observed with greater frequency.

The basic divergence, however, derives from a different interpretation of the bronchoscopic findings. We wonder whether many holes or so-called fistulae included in the records of other authors, are not actually diseased excretory ducts. Pathologic changes in the bronchial glands with consequent cystic degeneration of the glands or enlargement of the ducts occur certainly much more frequently in the adult than perforation of caseous lymph nodes. Especially persons with long standing infections of the respiratory tract and certainly those suffering from pulmonary tuberculosis are liable to develop these changes. We saw, of course, such lesions also in non-tuberculous patients with chronic inflammatory changes in the respiratory tract, e.g. with chronic bronchitis, asthma and emphysema. Of the six autopsy specimens with the typical holes, five showed evidence of severe chronic bronchitis. With contrast filling of the bronchial tree, we were able to demonstrate the typical picture of ductal dilatation in a great many patients suffering from chronic cough, pointing possibly to a pathogenetic relationship.

Differentiation between lymph node perforation and enlarged glandular ducts is often difficult only on bronchoscopic appearance. In rare instances, an actual perforation may heal and present a normal mucosal covering. On the other hand, active pathologic changes may occur within enlarged mucosal ducts in the absence of lymph node perforations. Infectious material may gain entrance into the glandular duct from the bronchial lumen and give rise to inflammatory changes within the glands.

In doubtful cases one must not rely on one single bronchoscopy. Additional clinical and roentgenologic data must be evaluated before a definite opinion is formed. If, on control examinations, signs of inflammation disappear and the caliber of the opening remains unchanged for a long period the lesion is probably an enlarged duct.

A correct diagnosis of lymph node perforation is, however, of great importance since it has serious implications for the patient. Major operations e.g. may have to be postponed for months. An active perforation, persisting after resection may lead to reactivation or spread of the specific process. Careful bronchoscopic evaluation is therefore mandatory prior to operation and in doubtful cases, it is better to repeat the examination in order to ascertain the character of the bronchial lesion noted.

Lymph node perforation in the adult in all stages of the disease does, of course, occur though it is rare. Seven of our observations probably belong to this category. The bronchoscopic observations alone were highly suggestive and they were further supported by clinical and/or roentgenologic signs of active tuberculous disease in adjacent lymph nodes. In the eight

cases, showing only residual scars, there was found a distinct correlation between the scar and the dominant pulmonary lesion. In five of these cases a calcified lymph node could be seen adjacent to the bronchial scar. Still, there was no indication as to the time of the lymph node perforation. It might have taken place much earlier, even during childhood.

Conclusion

In our experience, perforations of tuberculous lymph nodes into the bronchi are rarely observed on bronchoscopic examination of the adult, especially in patients suffering from the chronic phthisic form of pulmonary tuberculosis. Mucosal holes, however, as seen through the bronchoscope are more frequent and are apt to be diseased excretory ducts rather than fistulous tracts from caseous lymph nodes. We doubt therefore, that reports of frequent bronchoscopic diagnosis of lymph node perforation are convincing proof for the validity of Schwartz' concept of re-infection tuberculosis. Further clinical, bronchoscopic and careful anatomic studies are necessary in order to decide whether perforations of lymph nodes in all stages of adult tuberculosis are so common as to require a change in our views concerning the pathogenesis of the disease.

SUMMARY

Seven hundred consecutive bronchoscopies were analyzed for evidence of lymph node perforation into the bronchial tree without finding a single case with the pathognomonic appearance. Lesions suggestive of perforation were seen in seven cases and eight presented characteristic scars. Additional clinical and roentgenologic data corroborated the diagnosis in these 15 cases.

Pathologic openings in the bronchial mucosa were found with about the same frequency as in other institutions (8 per cent). Bronchoscopic, roentgenologic and anatomic features of these lesions are reviewed and described and their pathogenesis is discussed.

The difficulties in the interpretation of the bronchoscopic appearances of fistulous tracts due to lymph node perforation and diseased excretory ducts of mucous glands are noted.

RESUMEN

Se hicieron 700 broncoscopias consecutivas en busca de evidencias de perforación de ganglios hacia el árbol bronquial sin encontrar un solo caso patognomónico por la apariencia. Se vieron lesiones sugestivas de perforación en siete casos y ocho presentaban cicatrices características. Los datos clínicos y roentgenológicos adicionales corroboraron el diagnóstico en estos 15 casos.

Se encontraron aberturas patológicas en la mucosa bronquial con la misma frecuencia aproximada que en otras instituciones (8 por ciento).

Remark: By the time this article was completed, another 400 bronchoscopies had been analyzed, bringing the total of patients examined to over one thousand. Whereas the relative number of mucosal holes remained fairly constant (7 to 8 per cent) we did not find a single case of definite or suspected lymph node perforation.

Las características broncoscópicas, roentgenológicas y anatómicas de estas lesiones son objeto de revisión y su patogenia se discute.

Las dificultades en la interpretación de la apariencia broncoscópica de los conductos fistulosos debidos a perforación ganglionar y la distinción con los conductos excretorios enfermos, se hacen notar.

RESUME

700 bronchoscopies consécutives furent analysées pour rechercher la preuve de la perforation ganglionnaire dans l'arbe bronchique sans qu'on puisse trouver un seul cas indiscutable. La perforation pouvait être suspectée dans sept cas et huit autres présentèrent des cicatrices caractéristiques. Des constatations cliniques et radiologiques supplémentaires furent en faveur du diagnostic dans ces quinze cas.

Ces perforations pathologiques de la muqueuse bronchique se présentèrent avec environ la même fréquence que dans les autres conditions (8%). Les caractéristiques bronchoscopiques, radiologiques et anatomiques de ces lésions sont passées en revue et décrites et l'auteur discute leur pathogénie.

Il signale les difficultés d'interprétation bronchoscopique des fistules imputables à une perforation ganglionnaire et des conduits excrétoires des glandes muqueuses.

ZUSAMMENFASSUNG

Es wurden 700 auf einander folgende Bronchoskopien analysiert auf Beweise einer Lymphknotenperforation in den Bronchialbaum ohne dass ein einziger Fall gefunden wurde mit pathognomonischen Erscheinungen.

Auf Perforation verdächtige Veränderungen waren in 7 Fällen zu sehen, und 8 boten charakteristische Narben. Zusätzliche klinische und röntgenologische Daten bestätigten die Diagnose in diesen 15 Fällen.

Pathologische Öffnungen in der Bronchialschleimhaut wurden in ungefähr derselben Häufigkeit gefunden, wie in anderen Anstalten (8%). Bronchoskopische, röntgenologische und anatomische Merkmale dieser Veränderungen werden besprochen und beschrieben und ihre Pathogenese diskutiert.

Die Schwierigkeit in der Deutung des bronchoskopischen Aussehens der Fistelgänge infolge Lymphknotenperforation und erkrankter Ausführungsgänge der Schleimdrüsen wird erwähnt.

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SECTION ON CARDIOVASCULAR DISEASES

Results of Open Heart Surgery with Elective Cardiac Arrest by Potassium Citrate in Patients with Congenital and Acquired Heart Disease*

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The use of elective cardiac arrest in combination with a pump oxygenator makes possible better surgical exposure of the internal structure of the heart than has ever before been achieved. Melrose[1] and associates in 1955 reported a simple technique for stopping the heart by the use of potassium citrate solution in laboratory animals. Work in our laboratory[2] confirmed that a mixture of twenty-five per cent potassium citrate solution, diluted one part to ten with blood, would produce complete asystole when injected into the coronary circulation.

The heart is isolated from the systemic circulation by occlusion of the vena cavae, and clamping the ascending aorta, after establishing the usual cannulations for maintenance of the circulation with a pump oxygenator. The potassium solution is injected into the root of the aorta proximal to the clamp, so that it rapidly perfuses the coronary circulation. Complete asystole, with a soft, flaccid heart, occurs as soon as total perfusion of the coronary artery bed has been accomplished. The heart remains in asystole until the aortic clamp is removed, permitting the potassium solution to be washed out of the coronary circulation by arterialized blood from the pump oxygenator. Adequate perfusion of the coronary arteries with arterialized blood, under essentially normothermic conditions, results in a prompt return of normal heart rhythm.

Achievement of adequate surgical exposure for as long as 60 minutes in a quiet, reasonably dry field, inside any of the heart chambers, appeared to offer nearly unlimited possibilities for the correction of intra-cardiac mechanical deformities. Since February, 1956, 80 open cardiotomies have been performed by Dr. Donald B. Effler and associates utilizing elective cardiac arrest and one of four different pump oxygenators under the supervision of Dr. Willem Kolff.

The purpose of this report of initial results, presented from the viewpoint of a medical observer, is to record the successful results, and point out some of the reasons for clinical failure. Diagnostic and technical surgical problems will be stressed because these are most easily recognized,

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but it is evident that some of the most difficult and unresolved aspects of the overall problem remain in the field of prolonged total body perfusion. A lively and healthy controversy, beyond the scope of this report, still rages among the proponents of various oxygenators, and supports the belief that a truly ideal method remains to be found.

The anatomic problems dealt with, and the mortality encountered in each group are listed in Table I. While the basic nature of the defect has an important bearing on surgical mortality, this does not reflect other important factors such as age, body mass, myocardial reserve, anoxia, pulmonary vascular disease, and degenerative changes in the systemic circulation, which often proved to be crucial factors in achieving success or failure within each group. The largest number of patients (62.5 per cent) had interventricular septal defects or Tetralogy of Fallot. Nine patients had acquired lesions, including one with an interventricular septal defect due to septal myocardial infarction. The remainder were congenital in origin. The patients ranged in age from two months to 58 years. Body weight varied between seven and 190 pounds.

Cardiac catheterization was performed on all patients pre-operatively. During catheterization, selective cardioangiograms were photographed on 35 mm. motion picture film at 54 frames per second, using a 5 inch image amplifier. This could not be done successfully in many adult patients with very large hearts, but proved to be helpful in establishing anatomic diagnoses in children.

TABLE I

Diagnosis	Patients	Survived	Dead
1. Interventricular Septal Defect	31	21	10
2. Tetralogy of Fallot	19	12	7
3. Interatrial Septal Defect			
(a) Ostium Primum with Mitral Regurgitation	4	2	2
(b) Ostium Secundum with Mitral Stenosis	2	0	2
(c) Ostium Secundum	2	1	1
(d) With Anomalous Pulmonary Veins	1	0	1
4. Valvular Pulmonic Stenosis			
(a) With Intact Septa	1	1	0
(b) With Interatrial Septal Defect	2	2	0
5. Infundibular Pulmonic Stenosis with Intact Septa	1	1	0
6. Aortic Stenosis			
(a) Congenital	2	2	0
(b) Rheumatic	5	1	4
7. Mitral Regurgitation			
(a) Ruptured Chordae Tendineae	1	1	0
(b) Congenital Cleft-anterior Leaflet	1	1	0
(c) Rheumatic	2	0	2
8. Corrected Transposition of Great Vessels			
(a) Single Ventricle	1	0	1
(b) Pulmonic Stenosis and Multiple Interventricular Septal Defects	1	0	1
9. Pulmonary Hypertension			
(a) Suspected Intra-cardiac Tumor	1	0	1
10. Transposition of Great Vessels	3	0	3
TOTAL	80	45	35

Interventricular Septal Defects

Thirty-one patients were selected for closure of interventricular septal defects. Utilizing cine-cardioangiography, an attempt was made to demonstrate the relationship of the aortic and pulmonary valve rings to the plane of the ventricular septum. Patients with evidence of more than 50 per cent dextraposition of the aorta, and those in whom the lesion anatomically was proved pre-operatively to be a single ventricle were excluded as candidates for surgery. Those with small shunts (pulmonary blood flow less than twice the volume of systemic blood flow) and resting pulmonary artery systolic pressures below 45 mm. Hg. were not considered surgical candidates.

Patients were divided into two groups depending on the presence or absence of severe pulmonary hypertension.

TABLE II—INTERVENTRICULAR SEPTAL DEFECTS WITH PULMONARY HYPERTENSION

(Pulmonary Artery Pressure Higher Than 70 Per Cent of Systemic Pressure)

				Pressure		Oxygen Pulmonary A-V Difference	
		Age	Weight	P. A.	F. A.	Systemic A-V Difference	Result
1.	H. K.	7 yrs.	50 lbs.	74/40	106/62	0.45/1.9	Defect closed
2.	J. M.	5 yrs.	26 lbs.	124/64	140/62	1.75/3.5	Defect closed*
3.	C. C.	3 yrs.	30 lbs.	80/16	115/60	1.4/4.4	Defect closed
4.	C. J.	2 yrs.	30 lbs.	75/33	95/54	1.0/2.4	Defect closed
5.	W. Z.	4 yrs.	29 lbs.	112/64	117/73	2.0/3.55	Defect closed
6.	M. E.	11 mos.	14 lbs.	87/30	78/44	2.9/5.5	Coarctation excised. Possible incomplete closure
7.	R. G.	4 yrs.	29 lbs.	76/35	92/68	0.9/3.2	Defect closed
8.	R. P.	4 yrs.	33 lbs.	84/41	102/52	1.6/4.05	Defect closed*
9.	L. C.	4 yrs.	29 lbs.	89/42	110/55	3.6/4.5	Died—congestive failure. Pulmonary vascular disease
10.	L. R.	2 yrs.	25 lbs.	88/2	104/48	7.6/3.0	Died—fibroelastosis. Pulmonary vascular disease
11.	M. D.	4 yrs.	35 lbs.	86/50	92/42	4.0/4.0	Died—congestive failure. Pulmonary vascular disease
12.	J. K.	6 mos.	9 lbs.	88/48	92/58	0.9/2.65	Died—anoxia. Pulmonary cystic disease
13.	J. P.	11 yrs.	58 lbs.	85/54	108/65	1.5/3.3	Died—subacute bacterial endocarditis
14.	N. W.	27 yrs.	125 lbs.	108/64	113/70	0.5/5.2	Died—single ventricle. Incomplete closure. A-V block

*Post-operative catheterization.

Fourteen patients (Table II) had measured pulmonary artery pressures which exceeded 70 per cent of systemic pressures. The relationship between pulmonary and systemic blood flows was carefully evaluated, and proved to be a most important factor in determining the presence or absence of irreversible pulmonary vascular disease. Actual blood flow measurements could not be made because many of the patients were too young to cooperate in the measurement of oxygen consumption. It was possible, however, to measure pulmonary and systemic arterio-venous oxygen differ-

TABLE III—INTERVENTRICULAR SEPTAL DEFECT WITH MODERATE PULMONARY HYPERTENSION
(Pulmonary Artery Pressure Lower Than 70 Per Cent Systemic Pressure)

		Age	Weight	Pressure P. A.	Pressure F. A.	Oxygen Pulmonary A-V O_2 Difference / Systemic A-V O_2 Difference	Result
1.	B. I.	16 mos.	16 lbs.	58/20	90/50	0.7/3.4	Defect closed
2.	R. M.	8 yrs.	41 lbs.	32/16	108/62	2.0/4.4	Defect closed
3.	J. G.	5 yrs.	38 lbs.	57/20	112/62	0.9/3.7	Defect closed*
4.	D. C.	3 yrs.	24 lbs.	35/14	112/62	1.7/4.3	Defect closed
5.	N. S.	3 yrs.	32 lbs.	66/20	134/60	0.4/3.3	Defect closed*
6.	K. B.	18 mos.	21 lbs.	54/21	102/55	0.8/3.3	Defect closed*
7.	R. D.	5 yrs.	34 lbs.	42/11	108/50	1.1/3.3	Shunt persists*
8.	M. H.	7 yrs.	40 lbs.	52/28	112/70	2.1/4.0	Defect closed
9.	C. E.	22 mos.	28 lbs.	55/20	109/50	1.75/2.3	Probable incomplete closure
10.	K. M.	3 yrs.	31 lbs.	67/21	110/50	1.1/3.0	Defect closed*
11.	M. C.	3 yrs.	32 lbs.	45/11	118/50	3.0/4.1	Defect closed
12.	P. L.	4 yrs.	37 lbs.	60/25	132/90	0.7/3.1	Defect closed
13.	F. G.	48 yrs.	152 lbs.	63/23	136/92	1.1/4.6	Septal infarction. Possible incomplete closure
14.	W. H.	15 mos.	21 lbs.	42/20	96/52	2.75/5.6	Died—right ventricle occluded
15.	B. R.	7 mos.	7 lbs.	42/22	87/43	0.9/3.3	Died—A-V block. Multiple I.V.S.D. plus I.A.S.D.
16.	T. P.	9 yrs.	38 lbs.	52/14	112/68	1.7/2.9	Died—respiratory acidosis. Severe kyphoscoliosis. Myocardial necrosis
17.	J. K.	3 yrs.	27 lbs.	68/20	102/58	3.3/5.7	Died—focal myocardial necrosis

*Post-operative cardiac catheterization.

ences. When the pulmonary A-V difference is lower than systemic A-V difference, pulmonary blood flow exceeds systemic flow, and high pulmonary artery pressures may be expected to fall with successful closure of the shunt. If the pulmonary A-V oxygen difference approximates or exceeds the systemic A-V oxygen difference, pulmonary hypertension is due to high pulmonary vascular resistance, and closure of the septal defect cannot result in a return toward normal dynamics. Three of the 14 patients with severe pulmonary hypertension presented this picture (Table II, 9, 10, and 11). All died in the immediate post-operative period. Of the 11 who demonstrated *high* pulmonary flows, three died; one of bacterial endocarditis (Table II, 13), one because he proved to have a single ventricle which was an impossible technical problem (Table II, 14), and one (a six month nine pound infant) of ventilatory insufficiency complicated by cystic disease of the lungs (Table II, 12).

Of eight surviving patients with severe pulmonary hypertension, clinical evidence of successful closure is present in seven. In two of these, anatomic correction has been confirmed by post-operative catheterization and cardioangiograms. One patient in this group shows clinical manifestations of a residual left to right shunt.

Of 17 patients with pulmonary artery pressures lower than 70 per cent of systemic pressures, 13 (76.4 per cent) survived operation (Table III).

Four patients in this group died four hours to seven days after operation.

1. (Table III, 14). This child had an anomalous papillary muscle or moderator band, which crossed but did not obstruct the right ventricular outflow tract pre-operatively. It was carefully preserved and the defect was closed. The child died in acute right heart failure eight hours later. At post mortem examination, the muscle was found obstructing the right ventricular outflow tract, which was reduced in diameter as a result of closure of the septal defect. Similar problems, encountered since, have been solved by excision of such moderator bands without recognizable sequellae.

TABLE IV—INTERVENTRICULAR SEPTAL DEFECT
(Pre- and Post-operative Catheterization Data)

		Arterial O_2 Per Cent Saturation	Pulmonary Artery Pressure	Systemic Pressure	Oxygen Pulmonary A-V O_2 Difference / Systemic A-V O_2 Difference
1. J. M. (5 yrs.) 9 mos.	pre-op.	86	124/64	140/62	1.75/3.5
	post-op.	94	41/11	110/55	2.8/2.8
2. R. P. (4 yrs.) 8 mos.	pre-op.	90	84/47	102/55	1.6/4.1
	post-op.	94	39/10	104/60	3.7/3.7
3. N. S. (3 yrs.) 7 mos.	pre-op.	88	66/20	134/60	0.4/3.3
	post-op.	95	30/13	132/64	3.2/3.2
4. K. M. (3 yrs.) 9 mos.	pre-op.	90	67/21	103/50	1.1/3.0
	post-op.	95	36/6	124/62	4.1/4.1
5. J. G. (5 yrs.) 7 mos.	pre-op.	92	57/20	112/54	0.9/3.7
	post-op.	96	31/13	118/60	2.8/2.8
6. K. B. (18 mos.) 7 mos.	pre-op.	84	54/21	102/55	0.8/3.3
	post-op.	90	18/9	100/58	2.55/2.55
7. R. D. (5 yrs.) 7 mos.	pre-op.	93	42/11	108/50	1.1/3.3
	post-op.	94	35/12	118/56	0.6/3.5

2. (Table III, 15). A seven month infant weighing seven pounds was known to have a diaphragmatic hernia in addition to separate interventricular and interatrial septal defects. At operation she proved to have two ventricular defects instead of a single one anticipated. Both septa were closed. After the heart was allowed to beat, she showed persistent hypotension, hypoxia, and A-V block. She never regained consciousness. Small body mass and inability to maintain adequate ventilation contributed to the problem.

3. (Table III, 16). This girl had severe kyphoscoliosis. Her septal defect was easily closed. Post-operatively she developed biochemical changes characteristic of severe respiratory acidosis. Despite every effort at mechanical assistance, this could not be controlled. On the fifth post-operative day, progressive congestive manifestations appeared and she died on the seventh day. Post mortem examination revealed severe focal myocardial necrosis, which to date, remains unexplained.

4. (Table III, 17). A three year old boy developed persistent supra-ventricular tachycardia four hours after a satisfactory sinus rhythm had been established. He died suddenly 10 hours after operation. Post mortem examination revealed medial hypertrophy of the pulmonary arterioles, but no intimal changes. There was severe acute focal myocardial necrosis, which is unexplained.

The latter two patients present a problem which we believe is related to artificial perfusion. We do not believe this is due to the use of potassium citrate, since we have seen it in patients who have had artificial perfusion without induced cardiac arrest.

Of 13 surviving patients with mild to moderate pulmonary hypertension, 10 have had anatomic closure of the defect. In two, clinical study indicates that incomplete closure has been obtained, and in one, post-operative catheterization demonstrated persistence of the defect.

Table IV shows the post-operative catheterization data of seven patients from both groups seven to nine months following operation. All but one have had excellent surgical results with gratifying reductions in pulmonary artery pressure and eradication of shunts.

Table V summarizes the results in 31 patients of both groups. In Group I (patients with severe pulmonary hypertension) no patient with low pulmonary artery flow survived the immediate post-operative period. On the other hand, the results in Group I patients with high pulmonary flows approximated those obtained in patients with lower pulmonary pressures. The presence of pulmonary hypertension, therefore, should *not* be considered a valid contra-indication to surgery unless it is also demonstrated that:

TABLE V—INTERVENTRICULAR SEPTAL DEFECTS—31 PATIENTS

GROUP I—Pulmonary Artery Pressure Higher Than 70 Per Cent of Systemic Pressure	No.	Survived		Dead	
		No.	Per Cent	No.	Per Cent
A. Low Pulmonary Blood Flow	3	0	0	3	100
B. High Pulmonary Blood Flow	11	8	72.8	3	27.2
TOTAL	14	8	57.2	6	42.8
GROUP II—Pulmonary Artery Pressure Lower Than 70 Per Cent of Systemic Pressure	**No.**	**Survived**		**Dead**	
		No.	Per Cent	No.	Per Cent
High Pulmonary Artery Flow	17	13	76.4	4	23.6
TOTAL—Groups I and II	31	21	67.8	10	32.2

1. Pulmonary artery blood flow is low because of far advanced pulmonary vascular disease.
2. The aorta or pulmonary artery is too far transposed to permit closure of the defect.
3. The patient has a single common vetricular chamber, which at present constitutes an impossible technical problem for surgical correction.

Tetralogy of Fallot

The 19 patients classified as Tetralogy of Fallot all had interventricular septal defects with one or more obstructions in the right ventricular outflow tract causing a systolic pressure gradient between the right ventricle and pulmonary artery. In some there was significant overriding of the aorta, but in most the aorta arose entirely from the left ventricle. Right to left shunts were present at rest in all but one patient. Two patients had co-existing left to right shunts. The type of stenosis was classified as valvular in two, infundibular in 10, infundibular and valvular in six, and infundibular with hypoplastic valve ring in one patient.

At operation this group of patients showed incredible variations in internal structure, and it has become progressively more evident that the goal of restoration to normal cardio-dynamics is more easily discussed than achieved. Seven patients (36 per cent) died five hours to 31 days post-operatively. The causes of death were defined as follows:

1. Agenesis of the left pulmonary artery was unrecognized by pre-operative studies. Death due to anoxia.
2. Persistent complete A-V heart block occurred following car-

TABLE VI—TETRALOGY OF FALLOT
(Pre- and Post-operative Catheterization Data)

		Pressures		Arterial O_2 Per Cent Saturation	Pulmonary A-V Difference / Systemic A-V Difference
		R. V.	P. A.		
1. R. B.	pre-op.	104/3	12/6	82	4.8/2.9
(6 yrs.)	13 mos. post-op.	38/2	37/25	97	3.5/3.5
2. P. B.	pre-op.	77/2	31/15	81	3.35/1.6
(5 yrs.)	9 mos. post-op.	27/2	27/13	97	3.9/3.9
3. R. W.	pre-op.	92/2	22/12	77	9.3/5.2
(9 yrs.)	6 mos. post-op.	87/7	44/10	92	2.7/3.8
4. M. C.	pre-op.	89/4	....	72	6.5/3.0
(14 mos.)	7 mos. post-op.	108/6	38/10	94	3.9/5.6
5. D. L.	pre-op.	108/6	17/2	88	5.7/4.6
(5 yrs.)	8 mos. post-op.	140/6	38/12	90	3.0/4.2
6. D. B.	pre-op.	104/3	....	81	9.7/6.0
(12 yrs.)	4 mos. post-op.	98/3	34/8	97	3.4/4.6
7. R. G.	pre-op.	116/6	24/12	74	10.1/6.5
(10 yrs.)	4 mos. post-op.	78/10	57/17	93	2.2/3.4
8. J. D.	pre-op.	115/9	35/17	92	2.3/3.2
(8 yrs.)	8 mos. post-op.	118/12	110/42	92	2.6/6.6

diac resuscitation in two patients. One died with hypotension, severe anoxia, and intractable bradycardia 12 hours after operation. The other died suddenly 31 days post-operatively after a slow and difficult recovery from operation.

3. Cerebral edema led to generalized muscle spasm, positive pyramidal tract signs, and death five hours post-operatively. There were no generalized systemic changes. The exact cause remains obscure.
4. Sudden death due to asystole 12 hours after operation occurred immediately following trachial aspiration. Post mortem examination revealed wide excision of infundibular pulmonic stenosis and closure of ventricular septal defect. There were no congestive changes. No obstruction was present in the tracheo-bronchial tree.
5. Rapid development of pulmonary congestive changes, hypoxia, and death 20 hours after operation occurred in one child. Post mortem examination revealed severe acute focal myocardial necrosis. The cause is unknown.
6. Persistent cyanosis, supraventricular tachycardia, and progressive pulmonary congestive changes occurred in one child who died 30 hours after surgery. Post mortem examination was not permitted.

Of 12 surviving patients, 10 show clear-cut evidence of *functional* improvement, as judged by disappearance of cyanosis and polycythemia, regression of digital clubbing, and a remarkable increase in physical capacity for exercise. We were concerned about an associated increase in overall heart size which has persisted in nine patients.

Eight patients have been catheterized four to 13 months since operation. Table VI summarizes the results of this study. Complete anatomic and physiologic correction has been achieved in two patients (Table VI, 1 and 2). In four patients (3, 4, 5, and 6) the interventricular septal defect remains open, and pulmonary blood flow has been increased because of a reduction in the severity of obstruction in the right ventricular outflow tract. A significant degree of stenosis persists, however, protecting the pulmonary vascular bed from the full effects of high pressure and flow. Patient number seven still has a large interventricular septal defect with more effective excision of his infundibular stenosis. He has moderate pulmonary hypertension. Although his cyanosis has disappeared, his activity tolerance has not improved in the same degree as that noted in the first six patients. Patient number eight developed congestive heart failure three weeks post-operatively. She still has a large septal defect with severe pulmonary hypertension because there is no residual obstruction at the pulmonary valve. Her functional status has deteriorated and a second attempt to close the septal defect is planned in the near future.

From the above it would appear that the severity of right ventricular outflow tract obstruction may be relieved, but that closure of interventricular septal defects in patients with Tetralogy of Fallot is a much more

difficult problem than that presented by uncomplicated septal defects.

It is our belief that failure to bridge the gap of the defect with a prosthesis is responsible for these technical failures. Although it is usually unnecessary and undesirable to use a foreign body for closure of uncomplicated ventricular defects, this course is now being followed in patients with Tetralogy of Fallot.

Interatrial septal defect was thought to be the primary lesion in nine patients who required elective arrest.

Ostium primum defects with mitral regurgitation have been encountered in four patients.

1. The significance of mitral regurgitation was not appreciated in a seven year old boy with a large left to right shunt at the atrial level. His septal defect was carefully closed, avoiding both the mitral and tricuspid valves. Post-operatively he had persistent A-V heart block and developed progressively severe pulmonary congestive changes which could not be controlled by medical management. Mitral regurgitation was recognized as the basic cause of his increasing difficulties, but his heart block and pulmonary status precluded re-operation. Post mortem examination revealed a cleft in the aortic leaflet of the mitral valve. His atrial septal defect was closed. The lungs showed hemorrhagic pulmonary edema.

2. A 12 year old boy presented a similar picture to that noted above. His atrial defect was closed and he rapidly developed congestive manifestations and orthopnea. Heart catheterization showed a rise in pulmonary artery pressure from 23/6 mm. Hg., before closure of his atrial defect, to 57/26 mm. Hg. Pulmonary artery wedge pressures rose from 8 mm. pre-operatively to 26 mm. His left to right shunt had been abolished. A second open cardiotomy was performed via the left atrium. A crescent shaped prosthesis was sutured over the medial commissure of the mitral valve around the valve annulus. This effectively controlled the localized type of regurgitation present. His recovery from the second period of elective cardiac arrest was remarkably prompt. His heart size has been reduced by 25 per cent. All congestive manifestations have disappeared.

3. Mitral regurgitation due to a grossly dilated mitral valve ring was recognized at operation in a 17 year old boy with an interatrial defect. The medial commissure of the valve was partially closed by direct suture. The atrial defect was closed. He developed pulmonary edema and died 18 hours later. Post mortem examination revealed that both suture lines were fragmented.

4. Mitral regurgitation was found to be present in a 50 year old man with an ostium primum defect. An Ivalon sponge prosthesis was sutured to the mitral valve annulus above the medial commissure, and the defect was closed. He has made an excellent recovery.

These patients demonstrate the importance of recognizing and correcting mitral regurgitation when it co-exists with interatrial septal defects. The combination is not unusual. Exact pre-operative diagnosis of this combination of lesions is at present difficult and unreliable. Careful examination of the mitral valve in every patient before proceeding with closure of interatrial defects appears to be the surest method of diagnosis available at this time.

Ostium secundum defects with mitral stenosis (Leutembacher's syndrome) have been encountered on two occasions.

1. A seven month infant weighing 10 pounds proved to have congenital mitral stenosis and a large interatrial septal defect with a left to right shunt at the atrial level. Congestive manifestations could not be controlled on medical management. The mitral valve was approached through the defect from a right atrial cardiotomy. The valve was split by finger fracture and the atrial defect was closed. Despite tracheotomy, it was impossible to keep the lungs adequately expanded and the child died on the sixth post-operative day. At post mortem examination the atrial defect was closed. The anterior commissure of the mitral valve was split 0.8 mm. and the valve opening was adequate. Pulmonary edema and atelectasis were the causes of death in this infant.

2. A 34 year old housewife, with a history of congestive manifestations of five years duration, had been at bed rest for two years. The heart was more than 80 per cent larger than anticipated. She had a large left to right shunt at the atrial level. At operation severe mitral stenosis, mild mitral regurgitation, and a large interatrial septal defect were found. The mitral valve was fractured and the defect closed. She appeared to be improving until the eighth post-operative day, when she expired suddenly. Adequate closure of the defect and a good mitral commissurotomy were demonstrated at post mortem examination. Microscopic study of the heart muscle showed the presence of acute focal myocardial necrosis. Death was probably caused by a ventricular arrhythmia.

Uncomplicated ostium secundum defects have usually been closed without the use of elective cardiac arrest. In two patients with unusually large secundum defects, potassium citrate was used. One recovered uneventfully. The second patient, a 37 year old woman, had a bidirectional shunt at the atrial level with pulmonary and systemic blood flows of nearly equal magnitude. Her pulmonary artery pressure pre-operatively was 146/60 mm. Hg.

The defect was closed. Post-operatively she did not develop progressive congestive manifestations as we feared. She complained of paroxysmal bouts of air hunger, and during these episodes became mildly cyanotic. On the fifth post-operative day, she had a convulsive seizure and died. Her atrial defect was 4.3 cm. in diameter. No other defect was present. Microscopic study of the lungs showed medial hypertrophy of the small pulmonary arterioles with intimal proliferation to the point of total occlusion in many areas. Her pulmonary vascular disease was irreversible.

Interatrial Septal Defect with Anomalous Pulmonary Veins

The diagnosis of anomalous pulmonary venous drainage to the right atrium from the right lung was established by pre-operative study in a 12-year-old boy. His interatrial septal defect was not demonstrated pre-operatively.

At operation the right upper and middle lobe pulmonary veins drained into the right atrium posterior to the superior vena caval orifice. A very high interatrial defect was found in close proximity to the anomalous vein orifices. Repair of the defect was accomplished by suture of the right atrial wall into the defect so that the pulmonary veins were directed into the left atrium.

Four hours after operation, he developed acute pulmonary edema and it was feared that thrombosis of the involved pulmonary veins had occurred. He died two hours later.

Post mortem examination demonstrated that the pulmonary veins were patent. Microscopic study showed severe acute focal myocardial necrosis. The most severe lesions were in the sub-endocardial area of the left ventricle. The cause of death was acute left ventricular failure.

Valvular Pulmonic Stenosis with Intact Septa

Since ventriculotomy is not required, elective cardiac arrest is usually not used for these patients. Occasionally, however, it may be helpful.

1. A 30 year old woman with congestive heart failure and more than 50 per cent cardiac enlargement due to pulmonic stenosis had severe tricuspid regurgitation as a complicating lesion. Her pulmonary valve was opened by the usual supra-valvular

approach. Her heart was arrested and her tricuspid insufficiency was corrected by direct suture of one commissure through a right atrial cardiotomy. She made an excellent recovery.

Valvular Pulmonic Stenosis with Interatrial Septal Defect

Elective cardiac arrest has been used in two patients with this combination of defects though it is usually not required.

Both patients made uneventful recoveries and are believed to be normal.

Infundibular Pulmonic Stenosis with Intact Septa

This lesion is encountered rarely. A pre-operative diagnosis of Ebstein's malformation of the tricuspid valve was made in a 42-year-old woman with congestive manifestations of 12 years' duration. She was found to have an intact ventricular septum with hypertrophied moderator bands extending across the inflow tract of the right ventricle. The pulmonary valve was normal. The obstructing bands, having the appearance of anomalous papillary muscles, were excised. The patient recovered, but time for adequate evaluation of the ultimate has not yet passed.

Aortic Stenosis

For several years the supra-valvular approach to mechanically severe aortic stenosis had been used, without resorting to the use of a pump oxygenator or elective cardiac arrest. Surgical evaluation and correction of these lesions was attempted on the basis of palpation of the valve from above, and left a great deal to be desired. It was anticipated that the use of a pump oxygenator and elective cardiac arrest would permit a much more definitive surgical approach to this lesion under direct vision.

Congenital Aortic Stenosis

Two patients, aged 11 and 18 years, have had aortic valvulotomy for congenital aortic stenosis. Excellent visualization of the valves was obtained. Satisfactory valvulotomies were performed without the production of aortic regurgitation, and they have made uneventful recoveries.

Rheumatic Aortic Stenosis

Rheumatic aortic stenosis has been approached on five occasions.

1. The first patient was a 35 year old woman with severe aortic stenosis who had been in congestive failure. There was no history of angina pectoris. The posterior commissure was incised to the valve ring. A second incision was made through the anterior cusp, which was not exactly in line with the adjacent commissure. One hour after operation, signs of severe aortic regurgitation appeared with a fall in diastolic pressure to zero. She died five hours later in pulmonary edema. Post mortem examination revealed aortic regurgitation due to incision of the anterior valve cusp. There was also far advanced coronary artery atherosclerosis.

2. A 31 year old man recently developed congestive manifestations due to calcific aortic stenosis. At operation two of the commissures were precisely incised. During the procedure the incision in the aorta extended downward toward the valve ring close to the orifice of the right coronary artery. The aorta was closed, but when the aortic clamp was removed to perfuse the coronary arteries, it was not possible to re-establish an effective heart beat. Post mortem examination revealed that a suture used in closing the aortic incision obstructed the right coronary artery.

3. A 53 year old man had syncopal attacks, severe angina pectoris, calcific aortic stenosis, and generalized arteriosclerosis. At operation the left subclavian artery was

used for arterial cannulation. Early in the period of cardiac arrest, he suffered a dissection of the aorta from the left subclavian artery extending proximally to within 2 cm. of the valve ring and distally down the thoracic aorta for a distance of 17 cm. where it terminated in rupture back into the aorta. The valvulotomy was completed hurriedly under stress. A normal heart rhythm was re-established. He died suddenly on the third day after operation after all vital signs had stabilized. Autopsy showed no evidence of bleeding from the dissecting aneurysm. The valvulotomy was inadequate. There was no evidence of myocardial infarction, but extensive atherosclerotic changes were present in all major branches of the coronary arteries. A ventricular arrhythmia is believed to have been the immediate cause of death.

4. A 41 year old man with severe angina pectoris of two months duration had calcific aortic stenosis. An aortic valvulotomy was performed without difficulty. On the second post-operative day, he suddenly developed pallor, became dyspneic, and died within 30 seconds. Post mortem examination revealed an adequate valvulotomy. Coronary atherosclerosis was present involving the proximal branches of all vessels with 30 per cent to 50 per cent occlusion. Death was due to cardiac arrhythmia.

5. A 58 year old woman had repeated syncopal attacks due to calcific aortic stenosis. She recovered from operation without incident. She has had no more syncopal attacks in the seven months since operation and has shown an excellent improvement in activity tolerance.

It is widely accepted that angina pectoris occurs as a result of severe aortic stenosis. When this lesion is present, and evidence of previous myocardial infarction is absent, we have been hopeful that correction of the valve lesion would result in improvement. From the above, it is evident that very severe arteriosclerotic heart disease may co-exist with aortic stenosis, and that angina in these patients may be due to this, rather than the valve lesion. Better diagnostic methods for defining the status of the coronary circulation in such patients are essential to the solution of this problem.

Mitral Regurgitation

Ruptured Chordae Tendineae.

1. A 54 year old man had never experienced major rheumatic manifestations. A heart murmur was known to be present since puberty and congestive manifestations had been evident for two years. Fluoroscopy demonstrated generalized cardiac enlargement and pulsations were seen in the pulmonary arteries. Heart catheterization showed a small left to right shunt at the ventricular level. Pulmonary artery pressure was 96/41 mm. Hg. A persisting left superior vena cava draining into the coronary sinus was demonstrated as an incidental finding. Operation was performed for correction of an interventricular septal defect. Exposure of the heart revealed a palpable thrill over the left atrium characteristic of mitral regurgitation. Direct inspection of the valve, through a left atrial cardiotomy, showed chordae tendineae of the medial valve cusp were ruptured. An elliptical Ivalon prosthesis was sutured around the mitral valve annulus over the medical commissure. Since operation, in October of 1956, congestive manifestations have cleared. His heart size has reduced from 17.2 cm. to a trans-cardiac diameter of 14.5 cm.

Rheumatic Mitral Regurgitation

The above experience, in addition to effective secondary operation on the cleft antero-medial cusp, described under interatrial septal defects, led to the hope that some patients with rheumatic mitral regurgitation might also be benefited.

Two attempts to correct rheumatic regurgitation were begun. Both patients were lost on the operating table due to dissecting aneurysm of the aorta from the site of faulty arterial cannulation, so that this problem remains untested in our experience. The first patient was cannulated from the left subclavian artery. In the second, the common femoral artery was used.

In perfusing adults, especially older patients in whom arteriosclerotic changes may be anticipated, it would appear wise to divide inflow from the pump, and use two arterial cannulations instead of the customary one. The peripheral vessels available cannot withstand the mechanical stress imposed by high velocity flows above 3,000 cc. per minute, which are required for adequate perfusion.

"Corrected" Transposition of the Great Vessels

Perhaps a more practical term to describe this fortunately uncommon anomaly would be "Transposition of the Vascular Pedicle."

Although the basic course of the circulation is normal, the aorta within the pericardium lies to the left and slightly anterior to the pulmonary artery trunk, giving the vascular pedicle an external appearance like that seen in transposition of the great vessels.

Two such patients have been operated upon. The pre-operative diagnosis in the first was interventricular septal defect. He proved to have a single ventricle which could not be effectively closed, and died immediately after surgery.

The second patient was thought to have infundibular pulmonic stenosis and an interventricular septal defect. At operation a large defect in the membranous portion of the ventricular septum was found, in addition to two smaller defects in the muscular portion of the septum. The pulmonary valve ring was a tiny hypoplastic structure above a grossly narrowed, cone like, right ventricular outflow tract. The ventricular defects were closed, but the tiny pulmonary valve ring could not be adequately corrected. The child died four hours after operation.

Neither of these patients was a suitable candidate for surgical correction since both presented anatomic problems that could not be effectively modified.

Pulmonary Hypertension

A 24-year-old woman gave a history of severe dyspnea and syncopal attacks which began to occur at the age of 20 after the delivery of her second child. She recalled no rheumatic symptoms. She developed progressively severe congestive manifestations and cyanosis during the preceding six months. Physical examination revealed a Grade IV systolic bruit with an easily palpable thrill loudest at the left sternal border. Cardiac catheterization revealed no evidence of an intra-cardiac shunt. Pulmonary artery pressure was 136/74 mm. Hg. and femoral artery pressure was 114/70 mm. Hg.

The barium filled esophagus showed abnormal displacement posteriorly and to the left at the level of the left atrium. It was finally decided to explore her in the hope of finding a tumor in the left atrium.

At operation, there were no valve lesions. No tumor was found. The septa were intact. She died three hours after operation. Post mortem examination revealed very severe pulmonary arteriolar disease. In retrospect, it is probable that she had amniotic embolization at the time of

delivery, and after recovering from the acute insult, went on to develop chronic cor pulmonale.

Transposition of the Great Vessels

Correction of transposition of the great vessels, using the technique postulated by Albert, was attempted in three patients, aged two months, two years, and nine years. The posterior aspect of the atrial septum is opened and displaced to the left, permitting pulmonary venous drainage to the right atrium. Vena caval flow is directed into the left atrium by the use of an appropriate prosthesis. In two patients, this objective was attained. In the third, the atrial septum was not displaced far enough to the left to transpose venous return from the left lung. In all three, a normal sinus rhythm was restored, but all died within four hours of operation with overwhelming pulmonary congestive changes and anoxia. Further attempts in this direction have been abandoned.

A-V Heart Block

Before actual clinical trial of elective cardiac arrest, it was feared by some that its use might increase the incidence of complete A-V heart block after open cardiotomy. This is known to carry an ominous prognosis, and has been associated with sudden death in post-operative patients weeks or months following surgery. This fear has not materialized in practical experience. It has been seen in nine of the entire group (11.2 per cent) and transiently in two cases (2.5 per cent) of the survivors. Of those who died, one with a single ventricle had complete A-V block before operation; one was a seven pound infant with two interventricular defects; one had unrecognized fibroelastosis in addition to an interventricular septal defect, and another proved to have a single ventricular chamber. These, basically inoperable mechanical problems, accounted for four (44.4 per cent) of the nine patients. A-V block occurred in two patients with ostium primum defects of the interatrial septum with mitral regurgitation, who were made worse by closure of the septal defect without correction of the valve lesion. In one of these it disappeared after a second operation corrected the valve. It was seen in two other patients with infundibular pulmonic stenosis and large interventricular septal defects, both of whom died after extensive infundibular resection. The remaining instance occurred in a patient with interventricular septal defect who showed unexplained low grade fever for 13 weeks after operation. In this patient, it finally disappeared 4 months post-operatively.

From the above it would appear that A-V block is associated with preexisting myocardial disease, surgical injury to the myocardium, or the presence of mechanical lesions which are too severe to be compatible with maintenance of an effective circulation. Certainly the use of elective cardiac arrest does not contribute to its occurrence.

Conclusions

From the experience described above it is believed the following conclusions may be drawn:

1. The use of potassium citrate in the production of elective cardiac arrest for open heart surgery is a routinely applicable procedure, which is completely reversible under the conditions described. It increases surgical efficiency without adding hazard to the patient. In no instance has its use been responsible for fatality in this series.

2. The high mortality rate encountered is a reflection of a combination of factors which include:

a. Errors in diagnosis.
b. Errors in judgment in the selection of patients.
c. Failures in immediate post-operative care, particularly with regard to atraumatic maintenance of adequate ventilatory function in infants and small children.
d. Surgical errors preventable in view of previous experience.
e. Surgical errors inevitable at present due to lack of a precise enough understanding of extremely complex and infinitely varied intra-cardiac pathologic anatomy.
f. Incomplete solution of the problems involved in total artificial perfusion.

The writer is not qualified to define potential improvements in the latter three categories, but in humility born of bitter and occasionally enlightening experience the following statements may be made with regard to diagnosis and selection of patients for surgery.

We are passing through the last phases of an era in which the diagnostic appraisal of complex intra-cardiac lesion was based on clinical findings supplemented by physiologic measurements which permitted "diagnosis" on the basis of deduction and reason. These things are not depreciated, and will continue to be of utmost importance, but they *are not* adequate to meet the present demands of practical intra-cardiac surgery. They must be supplemented by methods that define intra-cardiac structure in motion with at least the precision the pathologist is able to accomplish with the dead heart in his hand. Recent developments in x-ray technique, particularly in the field of image amplification combined with high speed motion picture photography, applied to study of the central circulation, appear to constitute at least a forward step in that direction[5]. There is reason to hope that further technical improvements in this field, combined with meticulous correlation of pre-operative, surgical, and post mortem findings will make possible a close approach to the ideal of absolutely precise anatomic diagnosis supplemented by routinely dependable evaluation of functional capacity.

If these goals can be attained, the problem of selection of patients for surgery will take care of itself, as the limitations and scope of open heart surgery are further defined by increasing surgical experience.

SUMMARY

Elective cardiac arrest, accomplished by perfusion of potassium citrate solution into the coronary circulation, has made possible excellent surgical exposure of intra-cardiac structures during open cardiotomy in 80 patients

with a wide variety of congenital and acquired lesions. The cardioplegic effect of potassium was reversed by perfusing the coronary arteries with oxygenated blood. In no instance was death or surgical failure attributable to the use of cardiac arrest.

Forty-five patients have survived. Reasons for death have been stated within the limits of our present knowledge. The post-operative status of surviving patients has been evaluated on the basis of clinical findings and, when possible, by heart catheterization and cinecardioangiography six to 14 months after operation.

Anatomic correction with restoration of normal function may be anticipated in patients with atrial or ventricular septal defects, provided complete absence of the septum is not encountered.

Severe pulmonary hypertension is not a contra-indication to closure of septal defects, if there is a large left to right shunt with increased pulmonary flow.

In patients with Tetralogy of Fallot, inadequate closure of the ventricular septal defect has been found in most instances when a prosthesis has not been incorporated into the defect. These patients have shown clear-cut evidence of functional improvement, with increased pulmonary blood flow and relief of arterial hypoxemia, but anatomic correction and restoration of normal cardiovascular dynamics has usually not been obtained.

Experience with this small group of patients emphasizes the need for further refinements in diagnosis, surgical technique, artificial perfusion and post-operative management before the ultimate potential of open heart surgery may be fully realized.

RESUMEN

La perfusión de una solución de citrato de potasio ha hecho posible obtener a voluntad la detención del corazón para lograr una exposición quirúrgica excelente de las estructuras intracardiacas durante la cardiotomía en 80 enfermos con una variedad de afecciones congénitas o adquiridas. El efecto cardioplégico del potasio se contrarrestó por la perfusión de las coronarias con sangre oxigenada. En ningúan caso fué de atribuirse la muerte a la detención cardiaca provocada o la insuficiencia cardiaca pudo atribuirse a esa misma causa.

Han sobrevivido 45 enfermos. Las causas de defunción se establecieron dentro de los límites de los conocimientos actuales. El estado post-operatorio de los enfermos sobrevivientes se ha estimado basándose en los hallazgos clínicos y cuando fué posible, por la cateterización cardiaca y por cineangiocardiografía de 4 a 14 meses después de la operación.

La corrección anatómica con restauración de la función normal puede preverse en los enfermos con defectos atriales o septo-ventriculares siempre que no se trate de ausencia completa del septum.

La hipertensión pulmonar severa no es una contraindicación a la oclusión de los defectos septales si hay un amplio paso de izquierda a derecha con aumento del flujo sanguíneo pulmonar.

En los enfermos con tetralogía de Fallot el cierre inadecuado del defecto del tabique ventricular se ha encontrado en la mayoría de los casos cuando una prótesis no se ha incorporado dentro del defecto. Estos enfermos han mostrado definida evidencia de mejoría funcional con aumento del flujo sanguíneo pulmonar y alivio de hipoxemia arterial, pero la corrección anatómica y la recuperación hospitalización prolongada pueden ser evitadas por la excisión cuando son asintomáticas, inactivas y esa excisión da una morbilidad y mortalidad mínimas.

Hubo complicaciones de importancia en 5 casos pero solo uno trajo como consecuencia el dejar de volver al servicio activo.

Hubo una muerte debida a shock postoperatorio de causa indeterminada. Setenta y nueve por ciento regresaron a servicio activo y como los cambios de actitud recientes consideran la necesidad de tratamiento de largo plazo de la tuberculosis se cree que más del 90 por ciento se rehabilitarán para continuar el servicio naval activo.

RESUME

L'arrêt cardiaque électif par perfusion d'une solution de citrate de potassium dans la circulation coronarienne a rendu possible une excellente mise en évidence chirurgicale des formations intra-cardiaques pendant une cardiotomie à coeur ouvert chez 80 malades atteints d'une gamme étendue de lésions congénitales ou acquises. L'effet cardioplégique du potassium fut combattu par la perfusion dans les artères coronariennes de sang oxygéné. En aucun cas la mort ou l'échec chirurgical ne put être attribué à l'emploi de l'arrêt cardiaque.

45 malades survécurent. La cause des décès a été déterminée dans les limites de nos connaissances actuelles. La condition post-opératoire des malades ayant survécu a été évaluée sur la base des constatations cliniques, et quand ce fut possible, par cathétérisme cardiaque et cinécardioangiographie, 6 à 14 mois après l'opération.

On peut compter sur une correction anatomique avec restauration de la fonction normale chez les malades atteints d'imperfection de la paroi de l'oreillette ou du ventricule, à condition qu'on ne rencontre pas une absence complète du septum.

Une hypertension pulmonaire grave n'est pas une contreindication à la fermeture des imperfections de la paroi, s'il y a un shunt important de gauche à droite, avec débit pulmonaire augmenté.

Chez les malades atteints de tétralogie de Fallot, dans la plupart des cas, on ne put obtenir une occlusion parfaite de l'anomalie du septum ventriculaire à moins de faire appel à une correction avec prothèse. Ces malades ont montré la preuve nette d'une amélioration fonctionnelle, avec augmentation du débit sanguin pulmonaire, et soulagement de l'hypoxémie artérielle, mais la correction anatomique et la restauration de la dynamique cardiovasculaire normale n'a généralement pas été obtenue.

L'expérience pratiquée sur ce petit groupe de malades souligne la nécessité de perfectionnements ultérieurs dans le diagnostic, la technique chi-

rurgicale, la perfusion artificielle et la conduite post-opératoire, avant que les possibilités de la chirurgie à coeur ouvert ne soient complètement obtenues.

ZUSAMMENFASSUNG

Elektiver Herzstillstand, begleitet von Durchströmung des Coronarkreislaufes mit Kalium-Citrat-Lösung ermöglichte ausgezeichnete chirurgische Darstellung von intracardialen Strukturen während offener Cardiotomie bei 80 Kranken mit einer beträchtlichen Vielzahl angeborener und erworbener Veränderungen. Die Herzlähmende Wirkung von Kalium wurde aufgehoben durch Durchströmung der Coronararterien mit Sauerstoffgesättigtem Blut. In seinem Fall war der Tod oder chirurgisches Versagen der Anwendung von Herzstillstand zuzuschrei ben.

Es überlebteb 45 Patienten. Die Todesursachen wurden dargelegt innerhalb der Grenzen unserer heutigen Kenntnis. Der postoperative Status der überlebenden Patienten wurde auf der Grundlage der klinischen Befunde ausgewertet, sowie, wenn möglich, durch Herzkatheterisierung und Cineangiocardiografie 6-14 Monate nach der Operation.

Eine anatomische Korektur mit Wiederherstellung der normalen Funktion kann erwartet werden bei Patienten mit Vorhof- oder Kammer-Septum-Defekten, sofern nicht völliges Fehlen des Septums angetroffen wird.

Schwerer pulmonaler Hochdruck ist keine Kontraindikation für den Verschluss von Septum-Defekten, wenn ein erheblicher Links-Rechts-Shunt besteht mit vermehrter pulmonaler Durchströmung.

Bei Kranken mit Fallot'scher Tetralogie ergab sich in den meisten Fällen ein unzureichender Verschluss des Ventrikel-Septum-Defektes, wenn nicht eine Prothese in den Defekt eingesetzt worden war. Diese Kranken zeigten eindeutige Anhaltspunkte für funktionelle Besserung mit vermehrter pulmonaler Blutzirkulation und Beseitigung der arteriellen Hypoxaemie; jedoch wurde für gewöhnlich eine anatomische Korrektur und Wiederherstellung der normalen Herz-Kreislauf-Dynamik nicht erreicht.

Die Erfahrung an dieser kleinen Patientenzahl unterstreicht das Bedürfnis nach weiteren Verfeinerungen in der Diagnose, der chirurgischen Technik, der künstlichen Durchströmung und postoperativen Behandlung, ehe das äusserst Mögliche in der Chirurgie des offenen Herzens in vollem Umfang Wirklichkeit werden kann.

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Experimental Coronary Artery Occlusion: Ventricular Fibrillation and Survival as Affected by Selected Drugs and Ionic Alterations*, **

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The effect of drugs and ions upon the normal heart and upon isolated myocardium has been thoroughly investigated and adequately documented. Increased interest in the application of these substances in a manner which approaches the abnormal clinical situation—that is, following coronary artery occlusion and in various arrythmias—has been demonstrated during the past few years. The stimulus for this recent investigative trend has come primarily from three sources: (1) Fibrillation following coronary artery occlusion and the efforts to devise means of permanently increasing collateral blood supply to the myocardium; (2) Cardiac arrest or ventricular fibrillation during surgery; and (3) Ventricular fibrillation during hypothermia.

This report concerns experimental myocardial ischemia produced by acute coronary artery occlusion, the influence of drugs and inorganic ions on survival rates and early fibrillation and the influence on certain ions upon other ions.

Materials and Methods

Adult mongrel dogs were used as the experimental animals. Following anesthetization with intravenous nembutal, endotracheal intubation was accomplished and the chest opened by an incision in the fourth inter-space. The left coronary, circumflex coronary, and left anterior descending coronary arteries were carefully demonstrated. A heavy silk ligature was placed beneath the anterior descending branch immediately adjacent to its origin. The loose ligature was threaded through a small plastic tube which was anchored to the pericardium at one end and brought out through the chest wall at the other end. Following closure of the chest wall, the ligature ends and plastic tube were placed subcutaneously, the animal was given penicillin and returned to his cage.

The following day the animal was again anesthetized, control electrocardiograms obtained, and control blood samples drawn for plasma pH, potassium, sodium, chloride, calcium and carbon dioxide tension. The animals were then divided into the following groups depending upon the drug or ion which was administered: (1) Control, one day postopera-

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tive—10 dogs—no infusion. (2) Control, 20 days postoperative—three dogs—no infusion. (3) Acidosis—five dogs—100-140mEq. hydrochloric acid in 400 cc. water. (4) Alkalosis—five dogs—140-150mEq. sodium bicarbonate in 400 cc. distilled water. (5) Hyperkaliemia—five dogs—30-45mEq. potassium chloride in 400 cc. distilled water. (6) Hypercalcemia—five dogs—1 gm. calcium chloride in 400 cc. 5 per cent dextrose in distilled water. (7) Excess sodium chloride—five dogs—4½ gm. sodium chloride in 500 cc. distilled water. (8) Procaine—five dogs—500 mgm. "Novacaine" in 400 cc. 5 per cent dextrose. (9) Papaverine—five dogs—30 mgm. papaverine intravenously. (10) Quinidine—five dogs—100 mgm. quinidine intravenously. Immediately following the infusion, electrocardiograms were again obtained and blood samples drawn for the determinations listed above. The ligature was tightened, completely occluding the left anterior descending coronary artery and electrocardiograms were obtained at frequent intervals to one hour postocclusion. If the animal still lived at the end of this period he was returned to his cage without further care. Early fibrillation as used in this communication denotes fibrillation occurring during the sixty minutes following coronary artery occlusion. Mortality was determined at the end of the first 24 postoperative hours. pH was determined on the Beckman model G pH meter. Calcium was determined by titration with EDTA. Sodium and potassium were analyzed on the Beckman direct reading flame photometer. Chlorides were determined by a modification of the Volhard method. Carbon dioxide tension was measured by the Van Slyke manometric technique.

Results

(1) Control. The mortality following ligation of the left anterior descending coronary artery has been reported on large series of dogs by others so that we considered it necessary to use only 10 animals occluded on the first postoperative day. The mortality in these 10 dogs was 80 per cent with 30 per cent of the deaths due to early fibrillation which occurred during the first 12 minutes following ligation.

(2) Control, 20 days postoperative. Of passing interest is the fact that this experiment was designed originally to allow the animal to recover from thoracotomy and dissection around the coronary artery. We soon found that if ligation were delayed following pericardotomy we failed to achieve any mortality. This point is borne out in three cases in which ligation was delayed for 20 days after thoracotomy. In this group there was no mortality and in two of the three animals there was no change in the electrocardiogram pre and postocclusion.

(3) Acidosis. Hydrochloric acid in the amounts used in this study produced an acidosis with a mean pH of 7.22 as opposed to a mean control pH of 7.37. This group of five animals suffered an 80 per cent mortality and 40 per cent fibrillation rate.

(4) Alkalosis. The mean pH was elevated to 7.62 from a mean control of 7.37 by the infusion of sodium bicarbonate. The mortality rate was 80 per cent and fibrillation rate 60 per cent.

(5) Hyperkaliemia. A mortality rate of 60 per cent and a fibrillation rate of 60 per cent resulted when the mean potassium was elevated to 6.24 mEq. per liter from a mean control of 3.7 mEq. per liter by infusion of potassium chloride.

(6) Hypercalcemia. The infusion of 1 gm. of calcium chloride elevated the serum calcium from a mean control of 5 mEq. per liter to 7.7 mEq. per liter. Mortality 80 per cent, fibrillation 60 per cent.

(7) Excess Sodium Chloride. Only 500 cc. of 0.9 sodium chloride was infused and this hardly represents an excess as demonstrated by the minimum rise in sodium and chloride. However, 100 per cent mortality and 80 per cent fibrillation resulted.

(8) Procaine. A mortality rate of 100 per cent and fibrillation rate of 100 per cent resulted when 500 mgm. of "Novacaine" was infused.

(9) Papaverine. The intravenous administration of papaverine, 30 mgm. yielded mortality and fibrillation rates of 60 per cent.

(10) Quinidine. A mortality of 60 per cent, and fibrillation of 60 per cent followed the intravenous administration of Quinidine, 100 mgm.

(11) Ions. The influence of infusion of certain ions and drugs upon the blood level of other ions is charted in Figure 1.

Discussion

One of the earliest stimuli for investigation of ventricular fibrillation arose as the result of this lethal arrythmia following coronary artery occlusion. Unfortunately, medical attempts at preventing fibrillation have met with no success despite the tremendous amount of investigative work devoted to the problem. Wiggers[1] in 1940 in discussing the mechanism of ventricular fibrillation following coronary occlusion found that a significantly smaller amount of electric current was required to fibrillate the heart following experimental coronary occlusion than normally. He theorized that spontaneous fibrillation during or following coronary occlusion was precipitated because usually innocuous ectopic stimuli became of precipitating level for the hyperirritable myocardium. Beck[2] employed the term "electrically unstable heart" in discussing the mechanism of ventricular fibrillation. He found that 90 per cent of all the people who die of coronary artery disease die because the heart becomes electrically unstable and fibrillates. The electrically stable heart is one in which oxygen saturation is uniform throughout, and this stability persists when the oxygen tension is reduced provided the reduction is uniform throughout the myocardium. The heart becomes electrically unstable and may fibrillate when the oxygen tension is not uniform throughout the myocardium; that is, when an area with decreased oxygen tension is surrounded with well-oxygenated myocardium or vice versa. If some substance could be given which would appreciably decrease the hyperirritability of the myocardium and the incidence of fibrillation following coronary occlusion, substantial progress would have been achieved. This was one of the clinical applications in mind when this project was undertaken.

The consistent level of coronary artery ligation in any study of mortality following coronary occlusion has been emphasized repeatedly. Our control mortality rate of 80 per cent is similar to that of others who have used the same location for coronary occlusion. Hahn[3] reported a mortality rate of 70 per cent following ligation of the descending ramus of the left coronary artery. Bakst[4] reported a mortality rate of 60 per cent when the same artery was ligated but mentioned that the higher survival rate might have been due to the high incidence of an accessory left anterior descending coronary artery which arose from the circumflex branch of the left coronary artery. Vineberg[5] noted a mortality rate of 90 per cent. McAllister[6] showed an immediate mortality rate of 70 per cent following ligation of the anterior descending branch in a group of 100 dogs. The incidence of early fibrillation is not so widely reported but Beck[2] noticed early fibrillation in 50 per cent of his animals at normothermic temperatures.

Because of the nature of this study utilizing various ions and drugs, it was important to determine the incidence of early fibrillation. Because

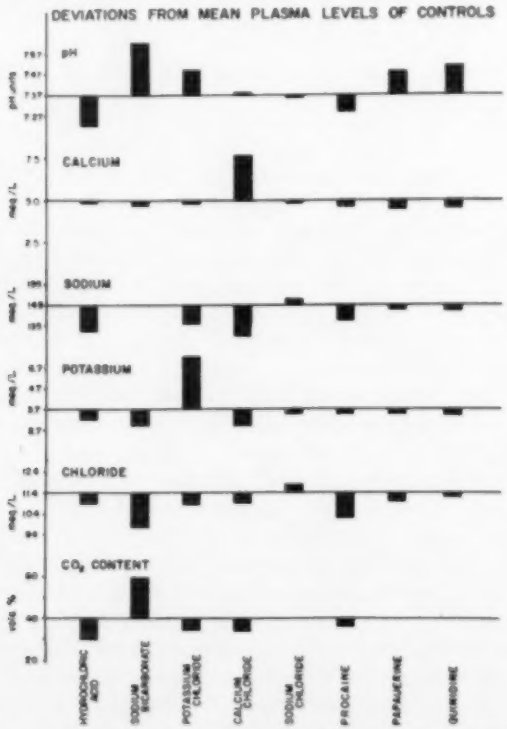

FIGURE 1: Plasma pH, calcium, sodium, potassium, chloride, and CO_2 content as affected by the ions and drugs employed in the study. The base line, from which the deviations are charted, represents the mean of the control determinations. Because of space considerations, these results are not discussed in the text and form the basis of a separate report.

these substances were administered only once immediately before coronary occlusion and were not administered to the surviving animals, a clear picture of the worth of the substance can be drawn from the early fibrillation rates rather than the overall mortality rates when the drug may have lost its effect. Our early fibrillation rate of 30 per cent is somewhat lower than that reported by Beck although the ultimate mortality rate is similar.

During the past several years efforts have been made along several lines to devise some procedure which would materially and consistently increase collateral blood supply to the myocardium. One of the earliest and still one of the relatively most successfully employed is the principle of irritation of the pericardium and myocardium to encourage collateral vessel growth to the myocardium. The three animals in this series whose coronary artery ligation was delayed 20 days following pericardotomy come under this category although no deliberate attempt was made to stimulate collateral vessel growth. It has been shown previously that simple pericardotomy offers significant protection to the animal when coronary occlusion is delayed for several days. In our series, in addition to opening the pericardium, a polyethylene tube and a large silk suture were left within the pericardium for 20 days. An additional stimulus for collateral vessel growth may have been bacterial pericarditis resulting from the clean, but not sterile, technique and propagated by the intrapericardial foreign bodies. In any event, we were surprised that the collaterals were of sufficient content as to prevent electrocardiographic evidence of coronary occlusion in two of the three animals, in addition to the survival of all three animals in the group. This group is of insufficient size to furnish any conclusions and, of course, was not originally designated for that purpose. However, it does point out the difficulty in evaluating some of the experimental results of other forms of myocardial vascularization.

During the past few years cardiac arrest or ventricular fibrillation occurring during an operation has been the subject of an ever increasing investigative effort. During the early years of these studies various anesthetic agents or combinations thereof were thought to be contributing factors toward ventricular fibrillation. However, during recent years carbon dioxide retention, acidosis and anoxia have been implicated as the contributing factors. With the advent of hypothermia, ventricular fibrillation attained even greater notoriety. It was essential that the incidence of ventricular fibrillation be greatly reduced or abolished if hypothermia were to continue in use as a procedure with acceptable risk. Few projects have been the subject of such intense investigation as has ventricular fibrillation in hypothermia. Certain investigators suggested that ventricular fibrillation might be used as an ideal state during surgery in the heart employing hypothermia and extracorporeal circulation. However, the majority of surgeons consider ventricular fibrillation a hazard worthy of avoiding. Cahn and Melon[7] reported the use of xylocaine anesthetization of the sinoauricular node as a means of preventing ventricular

fibrillation during hypothermia. Riberi, Siderys, and Shumacker[8] have effectively utilized procaine injection of the sin-auricular node. Webb[9] by injecting the auriculoventricular node with procaine, has achieved even greater protection against fibrillation.

While these measures have been successful, investigation along other lines has strongly implicated potassium as the excitatory agent for ventricular fibrillation. Harris[10] et al. injected potassium chloride solutions in varying concentrations into coronary arteries of dogs and noted that the intensity of ectopic ventricular activity depended upon the amount of potassium chloride present. Following coronary ligation, there was a large increase in the potassium content of venous blood from the ischemic area, increasing from a control level of 12.75 mgm. per cent to 24.5 mgm. per cent. The potassium concentration showed a positive correlation with the ectopic activity. In addition, potassium concentration reapproached control levels during the periods that corresponded to the times of disappearance of ectopic activity. At that time potassium content of the infarcted muscle was greatly reduced. Montgomery, Prevedel, and Swan[11] likewise obtained convincing evidence relating potassium and plasma pH to ventricular fibrillation. Hooker[12] found that ventricular fibrillation in the isolated perfused heart could be converted by the addition of potassium to the perfusing medium. Brown and Miller[13] produced ventricular fibrillation in 11 of 15 dogs by a rapid reduction in alveolar carbon dioxide tension following 4 hours of breathing 30 to 40 per cent carbon dioxide.

Our studies suggest that there is no correlation between serum potassium

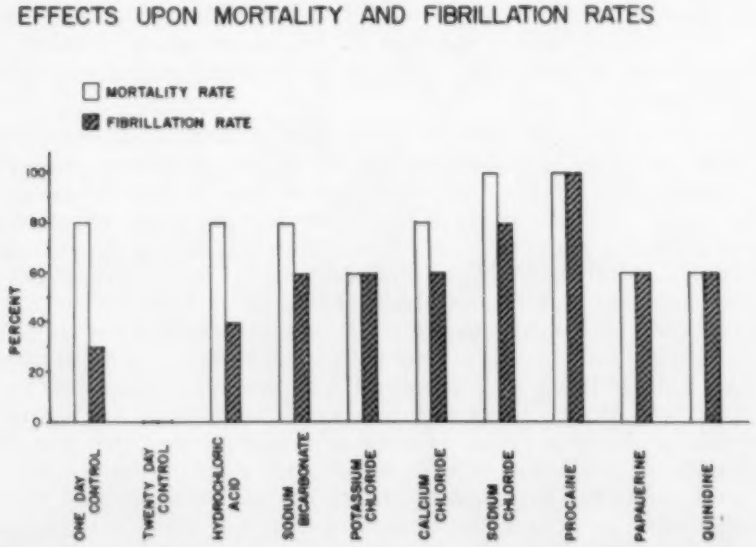

FIGURE 2: Mortality and fibrillation rates of the control and the various ion and drug series.

level and ventricular fibrillation. When Figs. 1 and 2 are inspected it is noted that when the serum potassium was lowest, as in the sodium bicarbonate and calcium chloride series, a fibrillation rate of 60 per cent occurred. When the serum potassium was considerably increased by the infusion of potassium, fibrillation again occurred in 60% of the animals. Thus it would appear that if potassium is the excitatory agent for ventricular fibrillation that myocardial potassium is unaffected by plasma concentration and is on a metabolic basis.

Grumbach[14] et al., using isolated rabbit hearts, studied ventricular fibrillation as related to calcium and potassium. Their results indicated that the initiation of fibrillation was dependent upon the calcium content in the tissue fluid which in turn was determined by the potassium content in the fluid. In our studies in which the serum levels of calcium and potassium were considerably increased, the 60 per cent fibrillation rate was the same in each although the ultimate mortality in the hypercalcemia group was slightly higher.

Bellet[15] in discussing the possible modes of action of 0.5 molar sodium lactate in preventing or correcting cardiac arrythmias considered that one of the beneficial actions of this solution might be due to the production of alkalosis. In this study, employing sodium bicarbonate rather than sodium lactate to obtain a significant alkalosis, the mortality rate following coronary occlusion was the same as the control but the fibrillation rate of 60 per cent was twice the control level. Thus, alkalosis as obtained with sodium bicarbonate, does not reduce the fibrillation rate which follows the demanding stimulus of coronary occlusion.

Montgomery's[11] observation showed that blood pH influenced the concentration of potassium in the myocardium, demonstrating that with a low pH the heart takes up potassium whereas with a high pH the heart maintains potassium balance. In our series the mortality and fibrillation rates in the acidosis group most closely approached the control levels whereas the alkalosis group demonstrated fibrillation rates twice the control levels although the ultimate mortality was the same. Again, if potassium is the agent inciting ventricular fibrillation, it would appear that myocardial metabolism of potassium in myocardial ischemia is unaffected by blood pH insofar as decreasing early fibrillation is concerned.

The mortality rate of 100 per cent and fibrillation rate of 80 per cent obtained when coronary occlusion followed infusion of 500 cc. 0.9 per cent sodium chloride is difficult to explain. It can be seen from Figure 1 that the elevation of sodium and chloride were minimal and that the other ions measured were not appreciably changed. In addition, the volume of fluid employed in the infusion was similar to that used in the other series.

The studies of Long[16] and associates show that the intravenous administration of procaine in normal dogs in increasing dosages produced successively, bundle-branch block, slowing of conduction through the A-V node, ventricular tachycardia, and ultimately ventricular fibrillation.

Their studies also suggested that in hearts with muscle damage cardiac changes occurred with therapeutic doses of procaine. Van Dongen[17] found that "Novacaine" was active against electrical fibrillation and its after effects and against heterotopic rhythms caused in other ways. Wiggers and Wegria,[18] employing cats' hearts and electrical stimulation, concluded that procaine raised the resistance of the ventricles to fibrillation but did not prevent its occurrence. In our study, in which coronary ligation rather than electric current was used as a stimulus, intravenous procaine was the most lethal agent used insofar as fibrillation was concerned with a 100 per cent mortality and 100 per cent fibrillation rate resulting.

In discussing antifibrillatory drugs, DiPalma and Schultz[19] showed that papaverine raised the threshold for ventricular fibrillation. In addition, papaverine intravenously was demonstrated to be a marked coronary dilator which was considered to be one of the reasons for its beneficial action in fibrillation. However, it was stated that papaverine might cause ventricular fibrillation in large doses. Elek[20] studied the effects of increasing levels of papaverine on the animal electrocardiograms. In addition he demonstrated that the favorable action of papaverine in reversing artificially induced ventricular fibrillation was due to depression of conductivity and irritability and to prolongation of the refractory period of the ventricles. In this present series, using 30 mgm. of papaverine intravenously, the fibrillation rate was twice the control although the mortality rate was slightly reduced.

Hess and Haugaard[21] studied the effect of quinidine on the carbohydrate metabolism of rat heart slices and homogenates. In varying concentrations quinidine produced marked inhibition of glucose utilization and oxygen uptake by homogenates. In some of the older medical literature[22-23] quinidine was believed to be beneficial in ventricular tachycardia following coronary thrombosis. Moissette,[24] studying the action of quinidine following occlusion of the descending branch of the coronary artery concluded that quinidine did not prevent ventricular fibrillation but on the contrary often favored it in the presence of coronary occlusion. Smith,[25] investigating the action of quinidine by a method similar to the one employed in this study, concluded that the dog's myocardium was rendered more susceptible to the development of cardiac irregularities by quinidine sulfate. The mortality rate in his series following occlusion of the left circumflex coronary artery was reduced from 75 to 55 per cent when large doses of quinidine were administered intravenously. The mortality and fibrillation rate of 60 per cent in our quinidine series would suggest that it favors the development of ventricular fibrillation.

SUMMARY

1. The effect of selected drugs and various inorganic ions on ventricular fibrillation and mortality following experimental coronary artery occlusion has been investigated.

2. Control mortality of 80 per cent and early fibrillation of 30 per cent

was obtained following ligation of the left anterior descending coronary artery immediately at its origin.

3. When coronary occlusion was delayed for 20 days post-pericardotomy in three animals there was no mortality and two of the three animals failed to demonstrate any change in the pre and postocclusion electrocardiogram.

4. Mortality of 80 per cent and fibrillation of 40 per cent resulted when acidosis was produced by hydrochloric acid.

5. Mortality of 80 per cent and fibrillation of 60 per cent resulted when alkalosis was produced by the infusion of sodium bicarbonate.

6. A mortality rate of 60 per cent and a fibrillation rate of 60 per cent resulted when hyperkaliemia was produced.

7. Hypercalcemia produced a mortality of 80 per cent and fibrillation of 60 per cent.

8. Following the infusion of a relatively small amount of sodium chloride an unexpected 100 per cent mortality and 80 per cent fibrillation rate resulted.

9. A mortality rate of 100 per cent and a fibrillation rate of 100 per cent followed the infusion of procaine.

10. The intravenous administration of papaverine produced mortality and fibrillation rates of 60 per cent.

11. Quinidine administered intravenously yielded a mortality rate of 60 per cent and fibrillation rate of 60 per cent.

12. The influence of infusion of certain ions and drugs upon the concentration of other ions was determined.

13. It would appear from this study that if potassium is the excitatory agent for ventricular fibrillation that myocardial potassium in ischemia is unaffected by the plasma concentration of potassium and is on a metabolic basis.

14. If potassium is the agent inciting ventricular fibrillation it would appear from this study that myocardial metabolism of potassium in myocardial ischemia is unaffected by blood pH insofar as decreasing early fibrillation is concerned.

15. None of the drugs or ions employed in this study showed any beneficial effect on reducing mortality or ventricular fibrillation following coronary artery occlusion.

We gratefully acknowledge the electrocardiographic interpretation of Dr. Thomas M. Blake.

RESUMEN

1. Se investigó el efecto de drogas seleccionadas, y de varios iones inorgánicos sobre la fibrilación ventricular así como sobre la mortalidad después de la oclusión coronaria experimental.

2. Se obtuvo el control de la mortalidad en el 80 por ciento y fibrilación temprana en el 30 por ciento después de ligadura de arteria coronaria descendente izquierda inmediatamente en su origen.

3. Cuando la oclusión coronaria fué retardada por 20 días después de la pericardiotomía en tres animales no hubo mortalidad y en dos de

los tres animales no se observó cambio alguno en el electrocardiograma antes y después de la oclusión.

4. Resultó una mortalidad de 80 por ciento y fibrilación de 40 por ciento cuando hubo acidosis provocada por ácido clorhídrico.

5. Una mortalidad de 80 por ciento y fibrilación de 60 por ciento resultó cuando se produjo alcalosis por infusión de bi carbonato de sodio.

6. Cuando se provocó hiperkalemia hubo una mortalidad de 60 por ciento y fibrilación de 60 por ciento.

7. La hipercalcemia produjo una mortalidad de 80 por ciento y fibrilación de 60 por ciento.

8. Después de una infusión de una cantidad relativamente pequeña de cloruro de sodio, resultó una inesperada mortalidad de 100 por ciento y fibrilación de 80 por ciento.

9. La mortalidad fué de 100 por ciento y la fibrilación de 100 por ciento, después de la infusión de procaína.

10. La administración intravenosa de papaverina produjo mortalidad y fibrilación en 60 por ciento.

11. La quinidina intravenosa dió una mortalidad de 60 por ciento y fibrilación de 60 por ciento.

12. Se determinó la influencia de la infusión de ciertos iones y drogas sobre la concentración de otros iones.

13. Parecería según este estudio que si el potasio es el agente excitador para la fibrilación ventricular, el potasio miocárdico en la isquemia no es afectado por la concentración del potasio en el plasma como lo es sobre base metabólica.

14. Si el potasio es el provocador de fibrilación ventricular parecería según este estudio, que el metabolismo miocárdico del potasio en la isquemia del miocardio no es afectado por el pH sanguíneo en lo referente al decrecimiento de la fibrilación temprana.

15. Ninguna de las drogas o iones empleados en este estudio mostró efecto benéfico alguno para reducir la mortalidad o la fibrilación ventricular después de la oclusión coronaria.

RESUME

1. L'auteur a examiné l'effet de médications choisies et de différents ions inorganiques sur la fibrillation ventriculaire et sur la mortalité consécutive à l'occlusion expérimentale de l'artère coronaire.

2. Il obtint de ramener le taux de mortalité à 80% et la fibrillation précoce à 30% après ligature de l'artère coronaire descendante antérieure gauche, immédiatement à son origine.

3. Lorsque l'occlusion coronarienne ne survint que 20 jours après la péricardotomie chez trois animaux, il n'y eut aucune mortalité, et chez deux des trois animaux on ne put mettre en évidence la moindre altération de l'électrocardiogramme avant et après l'occlusion.

4. Un taux de mortalité à 80% et 40% de fibrillation furent obtenus quand on créa une acidose par acide chlorhydrique.

5. Un taux de mortalité de 80% et de 60% de fibrillation fut obtenu lorsque on produisit une alcalose par injection de bicarbonate de soude.

6. Un taux de mortalité de 60% et un taux de fibrillation de 60% furent obtenus par l'hyperkaliemie.

7. L'hypercalcémie produisit une mortalité à 80% et 60% de fibrillation.

8. Après injection d'une quantité relativement faible de chlorure de sodium, un taux de mortalité inattendu à 100% et 80% de fibrillation se produisirent.

9. Un taux de mortalité de 100% et de 100% de fibrillation suivirent l'injection de procaine.

10. L'injection intraveineuse de papaverine produisit des taux de mortalité et de fibrillation de 60%.

11. La quinidine administrée par voie intraveineuse provoqua un taux de mortalité de 60% et un taux de fibrillation de 60%.

12. L'auteur détermina l'influence de l'injection de certains ions et médications sur la concentration des autres ions.

13. D'après cette étude, il apparaitrait que le potassium est l'agent excitateur de la fibrillation ventriculaire, que le potassium du myocarde dans l'ischémie n'est pas affecté par la concentration plasmatique de potassium et l'est sur la base métabolique.

14. Si le potassium est l'agent provocateur de la fibrillation ventriculaire, il apparaitrait d'après cette étude, que le métabolisme myocardique du potassium dans l'ischémie myocardique n'est pas affecté par le pH sanguin, au moins autant que le diminution de la fibrillation précoce est intéressée.

15. Aucune des médications ou des ions utilisés dans cette étude ne montra un effet bénéfique sur la réduction de la mortalité ou de la fibrillation ventriculaire après occlusion de l'artère coronaire.

ZUSAMMENFASSUNG

1. Es wurden die Wirkungen von ausgewählten Arzneimitteln und verschiedenen anorganischen Jonen bei Kammerflimmern und Tod nach experimentellen Coronararterienverschluss untersucht.

2. Eine Kontroll-Mortalität von 80% und ein frühzeitiges Flimmern von 30% wurden erzielt nach der Ligatur des vorderen absteigenden coronararterienastes unmittelbar an seinem Abgang.

3. Wurde der Coronarverschluss bei 3 Tieren aufgeschoben um 20 Tage nach der Pericardotomie, so gab es keine Sterblichkeit und bei² von den 3 Tieren war es nicht möglich, irgendeine Veränderung im EKG vor und nach dem Gefässverschluss nachzuweisen.

4. Eine Mortalität von 80% und ein Flimmern in 40% traten ein, wenn eine Acidose durch Salzsäure erzeugt wurde.

5. Eine Mortalität von 80% und Flimmern in 60% traten ein, wenn eine Alkalose erzeugt wurde durch die Infussion von Natrium-Bicarbonat.

6. Eine Mortalität von 60% und Flimmern in 60% traten ein, wenn eine Hyperkalaemie erzeugt wurde.

7. Hypercalcaemie führte zu einer Mortalität von 80% und Flimmern in 60%.

8. Im Anschluss an die Infussion einer relativ geringen Menge von Kochsalz ergab sich eine nicht erwartete Mortalität von 100% und Flimmern in 80%.

9. Eine Mortalitätsziffer von 100% und Flimmern in 100% folgte der Infussion von Novocain.

10. Die intravenöse Verabfolgung von Papaverin führte zu Mortalitäts- und Flimmer-Raten von 60%.

11. Quinidin intravenös zugeführte erbrachte eine Mortalität von 60% und Flimmern in 60%.

12. Es wurde der Einfluss der Infusion von bestimmtem Jonen und Arzneimitteln auf die Konzentration anderer Jonen bestimmt.

13. Es möchte nach dieser Untersuchung scheinen, dass Kalium der erregende Stoff ist für Kammerflimmern, dass das Kalium des Myocards bei der Ischaemie nicht beeinflusst wird durch die Plasma-Konzentration des Kaliums und zwar auf der Basis des Stoffwechsels.

14. Ist nun das Kalium der das Kammerflimmern antreibende Stoff, so würde sich aus dieser Untersuchung ergeben, dass der Kaliumstoffwechsel des Myocards bei der Ischaemie nicht beinflusst wird durch das Blut-pH, insofern das abnehmende frühe Flimmern betroffen ist.

15. Keine der Arzneimittel oder Jonen, die für diese Untersuchung verwandt wurden, zeigten irgendeine nützliche Wirkung hinsichtlich der Verringerung der Sterblichkeit oder des Kammerflimmerns im Anschluss an einen Coronar-Arterienverschluss.

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Therapy of Angina Pectoris

Evaluation of Anti-anginal Agents and Procedures

Angina pectoris has been defined as "paroxysmal chest pain of psychosomatic origin . . . caused by myocardial ischemia . . ."[1] It is a most changeable subjective manifestation with little consistent quantitative relation to the underlying coronary disease.[2] Silber and Katz[3] emphasize that angina pectoris is pain and, hence, must be analyzed according to the physiology of sensation, quite apart from factors having to do with coronary flow. As they state, "It cannot be shown that there is a high correlation between the ability of a drug to prevent electrocardiographic changes under stress and to prevent anginal pain."

Over 20 drugs and 10 surgical procedures have been advocated for the long-term treatment of angina pectoris. This suggests no one remedy is effective.

Assay of an anti-anginal agent or procedure is the measurement of a completely subjective sensation—the decrease in frequency and severity of chest pain. Although pain perception is fairly uniform from individual to individual, persons vary greatly in their reaction from time to time. Studies have shown pain to involve physical perception as well as psychological reaction. Since the effectiveness of an anti-anginal agent is based on a subjective report, the many factors that condition a patient's reaction must be taken into consideration. Variation in these factors causes attacks of angina to differ in frequency and severity under identical circumstances in the same and in different individuals.

Variation in the reaction factor and spontaneous remissions interfere with any classification of angina according to response to effort. Comparison of anti-anginal agents and procedures is difficult because each has been tried on patients who often have not been classified according to degrees of severity of angina.

In addition to its pharmaceutic action, every drug has a placebo effect that is derived from the urgent desire of patients for relief and from the physician's enthusiam. Thus the total drug effect is equal to its active effect plus its placebo effect. Placebos have been shown by Evans and Hoyle[4] to relieve the pain of angina pectoris satisfactorily in 38 per cent of their patients. Beecher[5] reviewed 15 studies involving over 1,000 patients in which placebos were found to have a degree of effectiveness measuring 35.2 plus or minus 2.2 per cent.

There is an inherent therapeutic effect of an agent or therapy proportionate to its impact on the psyche. Thus, an injection has a greater effect than a pill, and a surgical procedure, the greatest effect of all. The counterpart of a placebo in the evaluation of a surgical technic is the sham operation.

Besides the placebo effect of the pill or procedure, it has been shown that the physician-patient relationship decreases the frequency of chest pain in patients with angina without placebos.[6] It is essentially in the rapport period—the initial stages of therapy—that a good psychologic relationship is established between physician and patient.

As the double-blind technic by-passes the placebo effect, so multiple control periods in the post-rapport period circumvent the effects of the doctor-patient relationship.[7]

The number of suitable patients with stable angina usually is too small to be statistically significant, and the daily attack of chest pain too infrequent to allow per cent improvement (as an expression of decrease in frequency of attacks) to be an accurate measurement in the assay of anti-anginal agents or procedures.[8] The results of a study[9] in which an anti-anginal agent is stated to have produced 50 per cent improvement in 48 per cent of 23 cases should be compared with another study[8] of 24 cases, in which 63 per cent of the patients were improved 75 per cent, by the ceremony of drug research and good doctor-patient relationship, which were the only therapeutic factors operating.

Medical Treatment

The Long-Acting Nitrates

The currently most popular representative of this group is pentaerythritol tetranitrate (Peritrate), in 10 to 20 mg. oral tablets, three to four times a day. Peritrate was found by Winsor and Humphreys to be helpful in preventing anginal attacks, but neither multiple successive control periods nor the double-blind technic was employed. Russek et al. believe that Peritrate protects selected patients with coronary artery disease from electrocardiographic changes produced by an exercise test. They did not demonstrate, however, that Peritrate decreased the frequency of attacks of angina pectoris, a completely subjective manifestation. Salans, Silber and Katz, Friedberg and Talley, et al. found Peritrate ineffective in the treatment of cardiac pain. They found only one of 25 persons with angina pectoris to respond to Peritrate in the post-rapport period.

Another popular long-acting nitrate, triethanolamine trinitrate (Metamine) in daily doses of 6 to 16 mg. was reported by Palmer and Ramsey, and Fuller and Kassell as being effective in the prevention of anginal pain. In neither of these studies were multiple successive periods without medication provided as controls, nor was the double-blind technic employed. Silber and Katz, and Friedberg failed to find Metamine effective in the treatment of anginal pain. Friend et al.,[10] and Cole et al.[6] found Metamine to be ineffective when tested with the double-blind technic and multiple successive control periods.

The Xanthines

Gold et al.[11] traced the use of xanthine derivatives back to 1895 and commented that beneficial results in percentages of up to 80 per cent were from reports of clinical experiences rather than controlled investigations. Their experience agrees with that of Evans and Hoyle[4] who found that when xanthines were tested against placebo controls, the xanthines did not show

themselves to be worthy even of trial in the routine treatment of cardiac pain.

Oscharoff[9] claims that Elixophyllin in one to two ounce doses at four hour intervals is useful in the treatment of angina pectoris. He did not rule out, by utilization of the double-blind technic, the placebo effect or the cerebral effect of the alcohol of the elixir. Friedberg[12] has remarked that xanthine drugs have been marketed in combination with sedatives, usually phenobarbital, which may assure the benefit of at least one drug in the combination.

Khellin and Papaverine

The importance of the double-blind technic in by-passing the bias of the physician and the suggestibility of the patient in the evaluation of an anti-anginal agent is illustrated by Gold[13] in discussion of khellin. "When a physician knew which was drug and which was placebo, a large number of patients appeared to obtain relief of cardiac pain from khellin. When the study was repeated in the same group of patients, but neither physicians nor patients were aware of the identity of the agents, then the placebo and khellin could not be distinguished with respect to the effect on cardiac pain." Another group of investigators similarly had to reappraise their experience with khellin and with papaverine in angina when they retested these drugs employing the double-blind technic.[3]

Anti-thyroid Therapies

To reduce the patient's metabolism, diminish the work of the heart and its need for coronary flow, attempts have been made to ablate the thyroid gland by thiourea derivatives, radio-iodine and surgery.

The thiourea derivatives—mainly thiouracil, and propylthiouracil reduce the activity of the thyroid gland and are effective only so long as administered. They require prolonged therapy and have toxic effects, particularly on the hemopoietic system.

Radioactive Iodine

Where it is available, hypothyroidism is more easily induced by radio-iodine than by the thiourea derivatives or thyroidectomy. Blumgart et al.,[14] report 75 per cent of 720 patients to have worthwhile improvement. It should be noted that the good results are achieved at the expense of introducing myxedema, which has its own set of uncomfortable symptoms. For this, small daily doses (6 to 30 mg.) of thyroid can be administered to restore a metabolic rate consistent with comfort—usually minus 10 to minus 25 per cent.

Antithyroid therapies should be reserved for that small group of patients with angina pectoris whose symptoms are so severe that the introduction of myxedema is warranted. Since the symptoms of hypothyroidism would differentiate treated persons from the controls, double-blind technics are not applicable.

Surgical Treatment

Surgical procedures are indicated when severe angina has persisted for at least six months, or has become intractable despite every effort to elim-

inate or alleviate any possible contributory factor and all other means of treatment have been exhausted.

Operations on Nerves

All painful impulses pass through the upper four or five thoracic ganglia, their rami communicantes and the corresponding thoracic posterior spinal nerve roots. More successful results have been obtained by excision of the upper four or five thoracic ganglia than with paravertebral alcohol injections.

Production of a Collateral Blood Supply to the Heart

Currently the most popular surgical procedures are the Thompson, Beck I, Vineberg operations and the ligation of branches of the internal mammary artery. The Beck I operation consists of abrasion of the epicardium and lining of the parietal pericardium, application of an irritant, 0.2 gm. of powdered asbestos, to these surfaces, partial occlusion of the coronary sinus where it enters the right atrium and graft of the parietal pericardium and mediastinal fat to the surface of the heart. The Thompson procedure is the production of adhesions by the introduction of powdered silica (talc) into the pericardial cavity. While it is claimed that attacks of angina are prevented or diminished in frequency in 80 per cent of patients by the Thompson procedure, there is a 12 per cent operative mortality. Vineberg implants the internal mammary artery with an open freely bleeding intercostal branch directly into the left ventricular myocardium; 70 per cent improvement in 29 patients is reported.

That the impressiveness of the surgical procedure may be the major part of its therapeutic effect is suggested by Lillehei[15] who has applied the double-blind technic to the ligation of the internal mammary artery. His preliminary results indicate just as good results with the sham operation (skin incision) as with the operation itself. Ripstein[16] initially has found just as good results from the sham operation as from coronary vein ligation with or without poudrage.

Vineberg[17] has found that it is necessary to wait at least six months after surgery, beyond which the psychologic impact does not persist, before attempting to decide how much benefit the patient has obtained. He suggests careful before and after evaluations of the patients by three members of a team of medical men, one of whom is a psychiatrist.

Psychosocial Therapy

The vise-like pain of severe angina, a recurrent symbol of sudden death or incapacitating disease, must be actively combated by a positive approach. The patient should be assured that he is going to live, and of the probability of a long and productive life if he cooperates in the treatment. To be told that he is not going to die, is too negative; the word death should not enter into a discussion of his condition. The patient may be greatly encouraged by being informed that cardiac patients often outlive other people because they lead a more moderate life. He should be seen frequently so that his confidence is restored, and to give opportunity for the emotional tensions arising from his domestic life and occupation to be ascertained and properly handled. The patient's functional capacity should be measured against

the demands of his job by the physician or a work classification unit where available. Then he should be encouraged to live as near a normal life as he is able. Eskwith[18] used a good physician-patient relationship, tranquilizing drugs—e.g. meprobamate and phenobarbital—to help patients handle the emotional tensions arising from family and business life. With an over-all medical approach, he was able to improve 90 per cent, and restore 80 per cent of patients with angina pectoris to active employability.

It is quite probable that psychosocial therapy accounts for many of the good effects attributed to drugs, radiation to the thyroid, and surgery.

ADDENDUM

Since this paper was submitted for publication, Cossio and Master have reported that Iproniazid (Marsilid) has decreased the frequency of attacks of angina pectoris. If confirmed by the double-blind technic and trial through multiple control periods in the post-rapport stage, this avenue of therapy may be rewarding. (Cossio, Pedro: "The Treatment of Angina Pectoris and Other Muscular Pain Due to Ischemia with Iproniazid and Isoniazid." *Am. Heart J.*, 56:113, 1958), (Master, A.: Personal Communication.)

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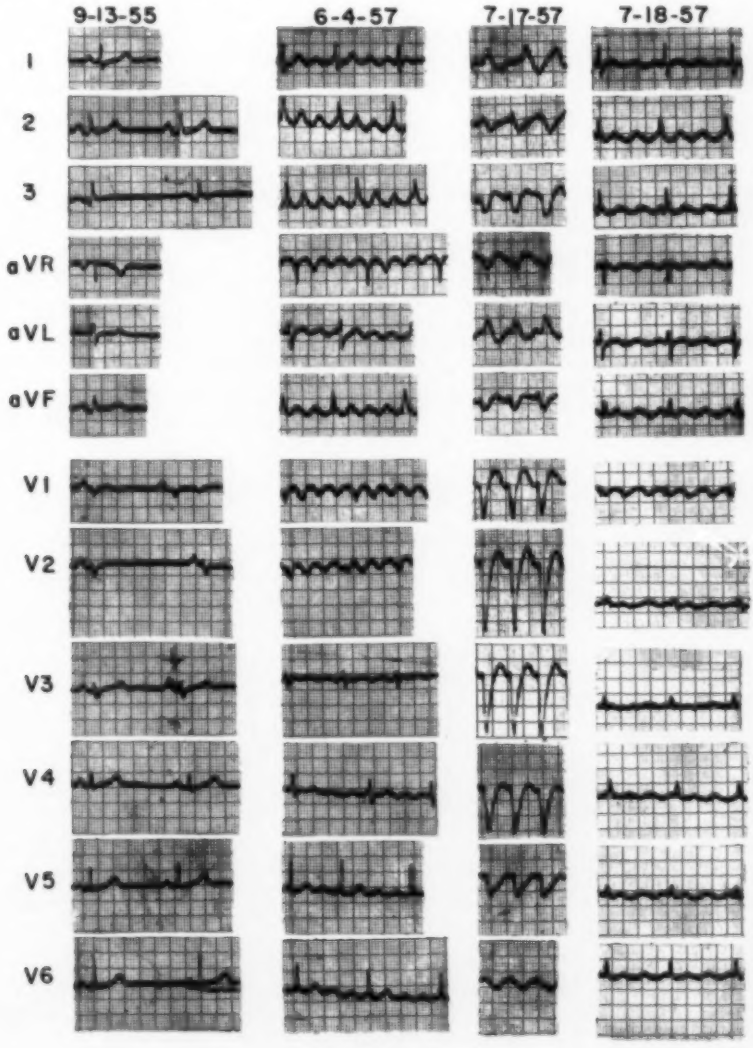
ELECTROCARDIOGRAM OF THE MONTH

The author would be pleased to receive comment and controversy from readers in relation to explanations offered.

Chronic Auricular Flutter

Mrs. A. H. is a 48 year old white woman who has mitral stenosis and aortic insufficiency with mild left ventricular hypertrophy noted in the chest x-ray. She has known about the cardiac murmurs since 1948. Her blood pressure is



130/60. She had normal sinus rhythm until 1955 (see illustration) and never required digitalis. On June 6, 1956 she was found to have 3:1 auricular flutter with a ventricular rate of 124 beats per minute and manifestations of decreased cardiac reserve. After appropriate digitalization, her cardiac reserve improved and the degree of a-v block increased to 5:1 with a ventricular rate of 64. The patient was given 0.2-0.4 Gms. of quinidine orally four times daily at home. About four days later normal sinus rhythm reappeared.

On June 4, 1957 (see illustration) she again had auricular flutter with a varying (3:1 and 4:1) degree of a-v block and congestive heart failure. After the latter had improved following regulation of digitalis intake, quinidine 0.5 Gms. four times daily was again administered while she was ambulatory for about one week. Auricular flutter did not disappear and she had symptoms of cardiac consciousness which were aggravated by anxiety regarding her domestic problems.

She was hospitalized and received anticoagulant medication as well as maintenance digitalis. Several days later, an attempt at reconversion to normal sinus rhythm was made by administering quinidine 0.4 Gms. every two hours for three doses. One hour after the last dose, she suddenly developed ventricular tachycardia with abnormally wide QRS complexes (see illustration July 17, 1957) together with mild peripheral circulatory failure and hypotension. These adverse manifestations disappeared spontaneously in about half an hour and auricular flutter (with 4:1 a-v block) reappeared as shown in the illustration (July 18, 1957).

Two months after this episode of quinidine toxicity, she still had auricular flutter with ventricular rate averaging 80 beats per minute. She is taking maintenance doses of digitalis only. The auricular flutter has remained despite a trial of other, and less toxic, dosage schedules of quinidine.

She has had chronic auricular flutter for almost one and a half years. Earlier, rather than later, in the course of auricular flutter, quinidine will often convert this arrhythmia to normal sinus rhythm although this is not a fixed rule. Such patients whom the author has followed do well when they are treated as though they had chronic auricular fibrillation, that is, when the ventricular rate is controlled with digitalis.

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Case Report Section

Subacute Cor Pulmonale Due to Metastatic Carcinomatosis of the Lung: Report of a Case with Autopsy Findings

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Introduction

Cor pulmonale is divided into the acute and chronic forms according to the duration of the disease. In the former the clinical picture of strain on the right side of the heart is manifested over a period of hours or several days and ends either fatally or in complete recovery of the patient. The commonest cause of this condition is pulmonary embolism. Chronic cor pulmonale is clinically manifested over a period of many months and is due to a multiplicity of causes such as valvular disease of the heart or chronic pulmonary disease. In 1937 Brill and Robertson[1] described a third form as subacute cor pulmonale in which the disease runs a fairly rapid clinical course extending over a period of several weeks during which severe dyspnea is the outstanding clinical symptom. In this paper we wish to report a case of subacute cor pulmonale and review briefly the literature on this subject in order to re-emphasize its clinical and pathologic features.

Report of a Case

A 58 year old housewife, mother of two, first came to the Lahey Clinic July 5, 1953. She had discovered a nodule in her left breast four years previously, and had done nothing about it. Recently it had become larger and caused mild discomfort. A nontender, fixed, hard, irregular mass was present in the left outer quadrant. Axillary lymph nodes were not enlarged.

Two days later a radical left mastectomy was done and the pathologic diagnosis was scirrhous carcinoma with metastases to 22 of 29 lymph nodes. Following operation she received 21 x-ray treatments from August 2 to September 2, 1953.

Periodic check-up examinations from 1953 on failed to reveal any recurrence until a visit on September 26, 1955, when she complained of cough, pallor and chest pain. Pressure elicited marked tenderness in the left axilla. Hemoglobin was 9 gm. per 100 cc., hematocrit 27, red blood cell count 3,010,000, white blood cell count 3,750, and the differential count was normal. The chest roentgenogram showed slight fibrosis in the left upper lobe, slight cardiac enlargement and increased density in the ribs. A film of the left ribs showed fracture of the eighth in the posterior axillary line. A roentgenogram of the spine, two weeks later, revealed spotty demineralization suggestive of metastatic disease. She received five x-ray treatments over the spine with moderate relief of upper back pain. Oreton methyl tablets, 10 mg. every other day, for 20 doses was also prescribed.

The first definite evidence of osseous metastases was in a skull roentgenogram on December 2, 1955, which showed a mottled destructive change throughout the entire calvarium with a large radiolucent area in the left supraorbital region. A chest roentgenogram gave the same appearance of mild fibrosis as previously. Her complaints were exertional dyspnea and moderate discomfort in chest and spine.

There was gradual increase in the dyspnea and on January 19, 1956, it was so severe she was brought to the hospital by ambulance. On examination she was cyanotic and severely dyspneic, struggling to breathe. Oxygen by nasal catheter gave no perceptible

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relief. She was too ill to have pulmonary function tests, but it seemed by auscultation that lung volumes were normal and it was not obvious why there was such respiratory difficulty. A chest roentgenogram again showed mild fibrosis as before, but in both lungs now. The heart was slightly enlarged and the vascular shadows prominent.

Treatment was symptomatic with oxygen and small doses of narcotics. There was increasing cyanosis, and the uncontrollable dyspnea continued until she died 46 hours after admission. The clinical diagnosis was carcinomatosis invoiving the skull, ribs, and vertebrae secondary to carcinoma of the breast; cor pulmonale secondary to pulmonary fibrosis secondary to x-ray therapy, and terminal pneumonia.

FIG. 1

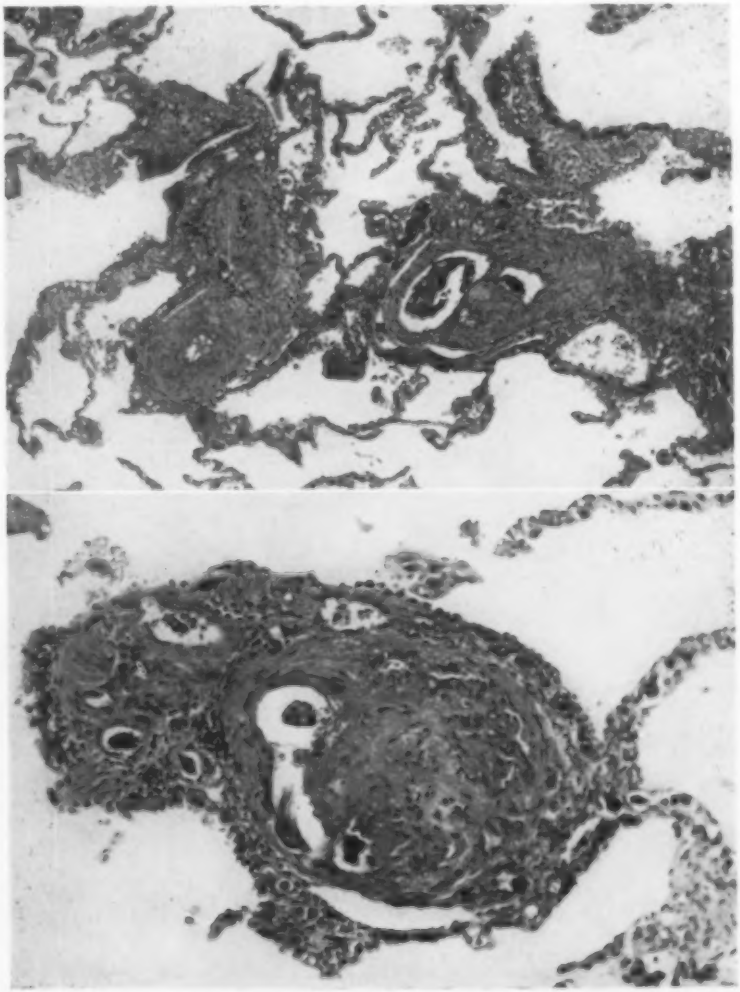

FIG. 2

Figure 1: This section of lung shows two small pulmonary arteries with a narrowed lumen due to a greatly thickened intima and occlusion of a third artery by tumor emboli and an organized thrombus.—*Figure 2:* Cross section of a small pulmonary artery showing an organized obliterating thrombus with tumor emboli. Note the presence of tumor cells in the perivascular lymphatics.

*Autopsy Findings**

External examination revealed the body to be that of a moderately obese elderly woman with a left radical mastectomy scar and signs of chronic lymphedema in the left arm. There was no evidence of recurrent tumor at the operative site. However, two small tumor nodules were palpable over the occiput. The neck veins were distended, and the ankles showed a mild pitting edema. Examination of the peritoneal cavity disclosed a distended stomach but no signs of metastases. When the sternum was removed, voluminous lungs were seen filling the pleural cavities and approximating each other in the midline. Each pleural cavity was free of fluid. The lungs were bound posteriorly and laterally by several thin fibrous adhesions. The right lung weighed 350 gm., the left 430 gm. Each lung was distended, crepitant and fluffy throughout except for minimal marginal atelectasis. Each showed glistening gray pleural surfaces with minimal anthracotic pigmentation. A fine granularity was noted over the right lower lobe and the anterior surface of the right upper lobe. Each lung presented a grayish, dry and almost bloodless cut surface with the exception of several subcrepitant, firm, dark red to green areas of discoloration in the right upper and left lower lobes. The bronchi contained a small amount of greenish mucoid material. There were no distinct tumor masses in the lung, and the peribronchial and paratracheal lymph nodes were grossly free of metastases. The larger branches of the pulmonary artery showed deposits of lipid in the intima.

When viewed *in situ* the heart appeared to be somewhat enlarged due to a prominent right ventricle and pulmonary conus. The venae cavae and the innominate veins were distended with blood. A transverse section through the ventricles resulted in the outpouring of an excess of fluid blood from the right side of the heart, yet exploration of the pulmonary artery and its major branches revealed no emboli.

The heart weighed 380 gm. The right auricle was slightly dilated and hypertrophied. There was also slight dilatation of the tricuspid valve which measured 10.5 cm. The right ventricular wall measured 0.4 gm. in thickness along the inflow tract. Its papillary muscles were large and the trabeculae carneae were broad and thick. The wall of the pulmonary conus was also hypertrophied and the trabeculae carneae were flat. The pulmonary valve leaflets were unaltered, and the dilated valve measured 8.2 cm. Changes in the left side of the heart included minimal dilatation and hypertrophy of the left ventricle which measured 1.4 cm. in thickness. The coronary arteries showed mild nonocclusive atherosclerosis.

Examination of the organs of the abdomen disclosed no evidence of metastatic tumor. Metastases were present, however, in the lumbar vertebrae and the left eighth rib.

Microscopic Examination

The significant histologic findings were present in the lung and bones. In the sections of lung taken from all five lobes, some of the small pulmo-

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nary arteries, arterioles and most of the lymphatic vessels were obstructed by masses of well preserved and apparently viable tumor cells. These cells were also present in alveolar capillaries. In addition, old organized thrombi with or without tumor emboli partially or completely occluded the lumen of some of the small pulmonary arteries, while others showed a narrowed lumen as a result of concentric intimal fibrosis (Figs. 1 and 2).

Although a considerable number of the small arterial branches showed these obstructive lesions, there were vessels that appeared to be spared. A moderate degree of emphysema and focal atelectasis was present, and there was evidence of terminal aspiration of gastric content with no inflammatory response.

The vertebral bones were the site of metastatic tumor with fibrosis of the marrow and hyperplasia of the cancellous bone. Tumor cells were demonstrable in many of the blood sinusoids.

The anatomic diagnosis was: status following left radical mastectomy for carcinoma of the breast; pulmonary carcinomatosis with cor pulmonale; metastatic carcinoma involving lumbar vertebrae, left eighth rib and skull; chronic lymphedema of the left arm; agonal aspiration of gastric content.

Comment

The Clinical Picture of Subacute Cor Pulmonale

The outstanding clinical features presented by this case were severe dyspnea and cyanosis not relieved by the administration of oxygen, the presence of linear shadows in both lung fields and slight enlargement of the heart in roentgenograms, and a clinical course of several months' duration. These signs and symptoms occurred in a patient with evidence of a metastatic tumor in the skeletal system and with a negative history of previous cardiopulmonary disease. The picture here was one of a rapidly progressive cor pulmonale in which the underlying cause was not evident ante mortem.

In 1937 Brill and Robertson reported a case and reviewed two others that presented this general clinical pattern with the exception that the primary tumors were gastric in origin and not diagnosed clinically. They designated this clinical picture of rapidly progressive failure of the right side of the heart as subacute cor pulmonale to distinguish it from the acute and chronic forms. Subsequent case reports[3, 4] have appeared in the literature under this title, each showing this general clinical pattern.

The Pathologic Substrate of Subacute Cor Pulmonale in Pulmonary Carcinomatosis

The gross autopsy findings in the present case report were meager indeed. There was evidence of pulmonary hypertension in the form of dilatation and hypertrophy of the right side of the heart with no obvious gross lesion to account for it. Careful inspection of the lung revealed the linear white streaks of dilated lymphatics and a fine granularity within the substance of the lung. The cause of the pulmonary hypertension became evident in the histologic sections in the form of obstructive lesions involving

the pulmonary arteries. These lesions were of three types: (1) organizing arterial thrombi with or without the presence of tumor emboli, (2) tumor emboli lodged in the lumen of small arteries and arterioles, and (3) pulmonary arteriosclerosis of the obliterative endarteritic type.

These obstructive vascular lesions appeared to be related. The frequent occurrence of tumor cells in organizing thrombi suggested that the latter may have been initiated by the presence of the former. Furthermore, the location of obliterative endarteritis proximal to points of obstruction in the longitudinal views of arteries suggested a causal relationship between the two lesions. This view is in opposition to that expressed by von Meyenburg,[6] Greenspan,[2] Brill and Robertson[1] who considered the obliterative endarteritis as an effect of perivascular lymphatic carcinomatosis. Wu's[7] objection to this explanation was based on the observations that only a few cases of lymphatic carcinomatosis showed these arterial changes and that even in these, many vessels were exempt. That the cor pulmonale was related to the obstructive arterial lesions and not directly to lymphatic carcinomatosis was borne out by the studies of Morgan.[5] He found that out of 78 cases of diffuse carcinomatosis of the lung only 11 showed right ventricular hypertrophy and of these, 10 showed obstructive arterial lesions in the form of vascular fibrosis or recent thrombosis.

It would appear then that the clinical picture of subacute cor pulmonale resulted when a sufficient number of pulmonary arteries were progressively obstructed by tumor emboli and thrombosis with the resultant obliterative endarteritis producing progressive increments of pulmonary hypertension that proved fatal within a matter of weeks.

Sites of the Primary Tumor in Reported Cases of Pulmonary Carcinomatosis

The primary site of the tumor in the majority of the reported cases was the stomach. Other primary sites included bronchus, breast, prostate, pancreas, large bowel, biliary tract and rectum. Since the primary tumor frequently remained undiagnosed during the life of the patient and since the symptomatology of subacute cor pulmonale is sufficiently distinctive, the presence of the latter should alert the clinician to the possibility of an occult malignant tumor that had metastasized to the lung in the form of diffuse vascular carcinomatosis.

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Metastatic Pulmonary Melanoma of 15 Months' Duration

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The lung is a common site for metastatic foci from extrapulmonary malignancies. Abrams[1] found the lung involved, metastatically, in 46.5 per cent of 1,000 autopsied cases of carcinoma. On the basis of radiographic evaluation, Pendergrass[2] estimated the incidence of pulmonary metastases from all carcinomas to be 30 per cent and as high as 75 per cent from renal cancer. In general, the secondary deposits in the lung appear on the roentgen film as bilateral, multiple, rounded shadows of varying size and are the result of hematogenous embolic spread. The primary tumors usually associated with this type of lesion arise from the thyroid, genito-urinary tract, intestinal tract and bones.

Malignant melanoma commonly involves the lung by way of vascular spread but the relative rarity of the tumor usually precludes its inclusion in the differential diagnosis of pulmonary lesions. In a radiographic study of 314 cases of pulmonary metastases, Minor[3] found 15 secondary to melanoma. The average time that elapsed between the onset of the primary lesion and the appearance of pulmonary metastases was 32.5 months and the interval between appearance of the metastases and death was 4.1 months. Most of the patients with melanomatous pulmonary deposits are diagnosed in the preterminal stages of the disease. The following case of malignant melanoma is therefore of unusual interest in that there was roentgen evidence of extensive metastases 15 months prior to death, during the greater part of which time the patient was completely asymptomatic. The diagnosis of melanoma was established 14 months after the initial roentgen observation of the pulmonary nodules.

The patient was a 61 year old, white clerk who presented himself at the Union Health Center on August 22, 1952 for a routine check-up. There was no significant complaint. With the exception of post-nasal discharge of 20 years' duration he had enjoyed excellent health. The past history revealed an appendectomy at age 15. His parents had died of heart disease in the eighth decade. Three brothers were alive and well. His appetite was good; bowels were regular, once daily; there was no genito-urinary or cardiovascular symptom. The physical examination and routine laboratory studies of the blood and urine were negative. A routine chest x-ray film (Figure 1) disclosed several large round nodules involving both lung fields. A tentative diagnosis of metastatic carcinoma was made and he was referred to the Memorial Hospital for further study.

A comprehensive examination was made at the Memorial Hospital and repeated at the Mount Sinai Hospital. Roentgen examination of the genito-urinary tract, entire intestinal tract, gall bladder and bones failed to reveal a primary lesion. Bronchoscopy and esophagoscopy were negative. Cytologic examination of the sputum, bronchial washings, gastric washings and urine were negative. He was advised to undergo exploratory surgery of the thorax and the abdomen on different occasions but refused. Between hospital and clinic visits he continued working and had no complaint other than the anxiety induced by the medical interest in his condition.

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**Director of Pathology Service, New York City Department of Hospitals.

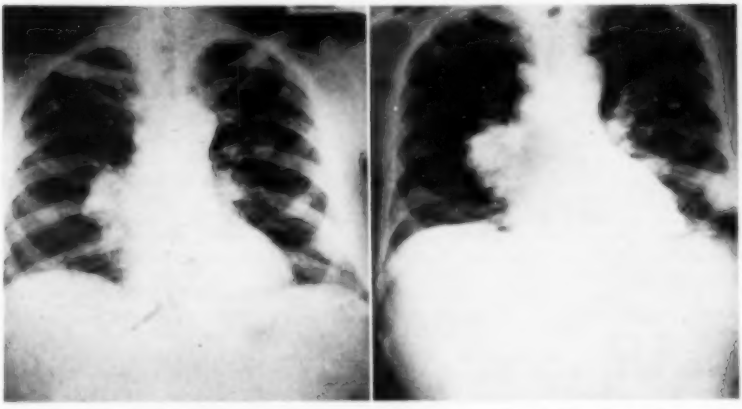

FIGURE 1 FIGURE 2

Figure 1: Routine chest film, August 22, 1955, showed large nodular densities in both lung fields. No pulmonary symptoms. (*Courtesy of The Union Health Center.*)—*Figure 2*: Films on October 5, 1956 (14 months later) showed a slight increase in the rounded densities previously observed. No pulmonary complaints during the interval between films.

Examination by one of us (M. B. R.) on May 1, 1956 found him to be well developed and nourished with evidence of recent weight gain. There were multiple pigmented nevi distributed over the thorax. The pupils reacted to light and accommodation and the external ocular movements were normal. The nasopharynx appeared negative. There were no palpable cervical or axillary nodes. The thorax was symmetrical, breath sounds vesicular and percussion note unimpaired. The cardiac outline was within normal limits, the sounds were of good quality, regular sinus rhythm, no murmur, ventricular rate of 80 per minute. The blood pressure was 140/80. There was a post-operative scar on the abdomen. The liver and spleen were not palpable. Rectal examination was negative. There was no peripheral edema. The reflexes were active and equal, bilaterally.

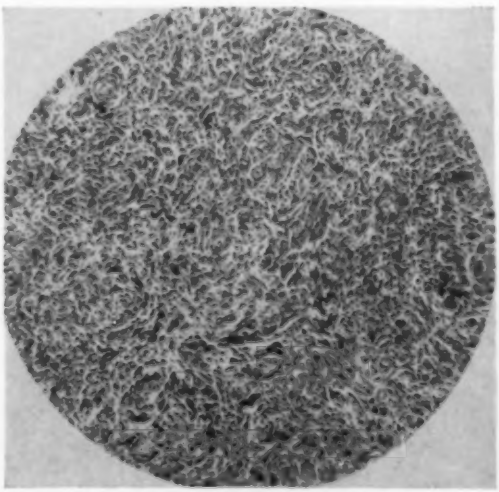

FIGURE 3: Metastatic melanoma of lung showing the marked anaplasia.

Roentgen examination of the chest showed no definite change in the number or size of the shadows seen on the film of August 22, 1955. The electrocardiogram showed left axis deviation. The sedimentation rate was 35 mm. per hour (Westergren). The blood count revealed hemoglobin of 82 per cent, 4,400,000 red blood cells, 9,750 white blood cells with normal differential. The urinalysis was negative. Intradermal tests were negative for coccidiomycosis and positive for histoplasmosis. Papanicolaou smears of the sputum were negative. The gastric washings were negative for tubercle bacilli.

He had no complaint until October 1956 when he suddenly became aware of spasmodic twitching of the right shoulder muscles and of the tongue. This was followed by weakness in the lower extremities, right hemiplegia and dysarthria. The pulmonary status was unchanged clinically and the roentgen examination (Figure 2) showed slight increase in the diameter of the nodular densities previously observed. He was admitted to the neurologic service of the Mount Sinai Hospital where a small pigmented area was noted on the lower lip near the buccal mucosa. Biopsy revealed the lesion to be a malignant melanoma. He was transferred to the Doctors Hospital on November 19, and died on November 26, 1956 after a series of convulsive seizures.

Necropsy examination revealed metastatic melanoma of the lungs, adrenals, jejunum, ileum, colon, ribs and brain. Gross inspection of the lungs showed tumor masses scattered throughout all the lobes. The masses were colored dark brown, were firm in consistency and measured up to 4.5 cm. in diameter. The right upper lobe contained one mass, the middle lobe had two, and the lower lobe four masses. The left upper lobe and lower lobe had four and five masses, respectively. The intervening parenchyma appeared normal. There was mild hyperemia of the trachea and main bronchi.

Microscopic examination showed the pulmonary masses (Figure 3) to consist of extremely bizarre cells having a spindle appearance and displaying anisocytosis, macronucleation, hyperchromatism and mitoses. There were focal areas of nests heavily pigmented by melanin. The non-tumerous portions of the lungs were normal.

The tumor masses in the adrenals were similar to those in the lungs and occupied the entire thickness of the cortex. In the intestinal tract, the tumors involved the muscle and submucosa and were about 2 cm. in size in the jejunum and ileum and smaller in the colon. The marrow of the third and fourth left ribs was diffusely brown to black and presented a striking appearance. The vertebrae were normal. The brain was deeply pigmented with the same cellular changes. In the cerebellum, the lesions were limited to the cortical gray and were characterized by necrobiosis and hemorrhage.

In all probability, the primary site of the melanoma was the lesion in the mouth, although this was not suspected for 14 months after the pulmonary metastases had been recognized. The large number of pigmented nevi scattered over the thorax probably contributed to the diagnostic confusion. It is also possible that in the course of the convulsive seizures, he had bitten his lip and drawn attention to the small pigmented area. According to Pack[4, 5] and Moore,[6] the oronasal region is an infrequent primary site for malignant melanoma, comprising approximately 2 per cent of the total. Origin from the lips is extremely uncommon.

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Editorial

A World of Peace

The traditional forms of education, political oratory, literature and religious ceremonies have conditioned the attitudes and spontaneous reactions of individuals and nations, and have created unnecessary barriers among them. Through science and natural philosophy we learn the truth or, to be more exact, with these aids at our disposal, we attain the most trustworthy conception possible of ourselves and the total nature of things. Scientific and philosophical knowledge aid man to gain wisdom and understanding.

Today, Kipling's oft-quoted couplet, "East is East and West is West, and never the twain shall meet" is irrevocably outdated. The situation presented by Kipling arose because the East, in its contemplation on aesthetic components of life, and the West in its pursuit of known components, tended to brand as illusory and evil any knowledge other than their own. There is no reason why the civilizations of the East and West cannot meet.

The international ideological issue today is not a simple question of good and bad, but a complex conflict between different conceptions of what is good. These different conceptions can be reconciled through personal contacts on international platforms. This will undoubtedly lead to intelligent appreciation and understanding of the ideological differences which are more imagined than real.

We want to live in a new sort of world, a world of peace. The flowering of science, which has rendered war absurd, also gives us wealth, comfort and freedom from disease in the body and mind. Our contest for position in the intricate fabric of society no longer need require that those who fail shall undergo suffering.

Medical science which is devoted to the alleviation of human suffering, is neither individual nor national, but international. Institutions and learned bodies devoted to scientific research are not concerned with Man's origin, his religion, race or country. Their doors are open to all. The international congresses on diseases of the chest, sponsored by the American College of Chest Physicians, afford excellent opportunities for the medical men and women throughout the world to meet, not only to exchange ideas on scientific matters, but also to create international good-will and understanding. Seeing other people and seeing ourselves as others see us, makes us wise. Wisdom leads to understanding. Understanding begets tolerance; tolerance, in its turn, leads to "Peace on earth and good will to all men."

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*Regent for India.

PROCEEDINGS OF THE 24TH ANNUAL MEETING

Board of Regents and Board of Governors

The Board of Regents and the Board of Governors of the College held their annual meetings on Wednesday and Thursday, June 18 and 19, at the Fairmont Hotel, San Francisco, at the time of the 24th Annual Meeting of the College. The following Regents, Governors, Chapter Delegates and guests were officially registered:

John F. Briggs, St. Paul, Minnesota, Chairman, Board of Regents
David H. Waterman, Knoxville, Tennessee, Chairman, Board of Governors

Osler A. Abbott, Emory University, Georgia
Crawford W. Adams, Nashville, Tennessee
William A. Adams, Chicago, Illinois
Malcolm L. Allan, Vancouver, British Columbia
Arnold S. Anderson, St. Petersburg, Florida
Robert J. Anderson, Atlanta, Georgia
Albert H. Andrews, Chicago, Illinois
Norman Arcese, Seattle, Washington
J. O. Armstrong, Dallas, Texas
Paul W. Auston, Langdale, Alabama
Carl C. Aven, Marietta, Georgia
Alvan L. Barach, New York, N.Y.
B. Guy Begin, Montreal, Quebec
Helen C. Bernfield, Jackson, Mississippi
Otto L. Bettag, Chicago, Illinois
Katharine R. Boucot, Philadelphia, Pennsylvania
Charles A. Brasher, Mt. Vernon, Missouri
Paul J. Breslich, Minot, North Dakota
Walter B. Brown, Livermore, California
Donald W. Close, Indianapolis, Indiana
Sumner S. Cohen, Oak Terrace, Minnesota
Lawrence R. Coke, Winnipeg, Manitoba
William S. Conklin, Portland, Oregon
Winthrop N. Davey, Ann Arbor, Michigan
Everett C. Drash, Charlottesville, Virginia
Seymour M. Farber, San Francisco, California
Max Fleishman, Omaha, Nebraska
M. Jay Flipse, Miami, Florida
Carl H. Gellenthien, Valmora, New Mexico
Roy F. Goddard, Albuquerque, New Mexico
Alfred Goldman, St. Louis, Missouri
Burgess L. Gordon, Albuquerque, New Mexico
William P. Gray, Batesville, Arkansas
Albert Guggenheim, Denver, Colorado
Joseph M. Hanner, San Diego, California
J. E. J. Harris, Albuquerque, New Mexico
Marvin S. Harris, Beverly Hills, California
W. Elliott Harrison, Vancouver, British Columbia
Thomas G. Heaton, Toronto, Ontario
George R. Herrmann, Galveston, Texas
George H. Hobbs, Mt. Vernon, Missouri
Corrin H. Hodgson, Rochester, Minnesota
Henry R. Hoskins, San Antonio, Texas
W. Leonard Howard, Northville, Michigan
Hollis E. Johnson, Nashville, Tennessee
Francis J. Kasheta, Glencliff, New Hampshire
Ray W. Kissane, Columbus, Ohio
Ross C. Kory, Milwaukee, Wisconsin
Alexander Libow, Miami Beach, Florida
Robert C. Locke, Reno, Nevada
Richard V. Lynch, Clarksburg, West Virginia
Arthur M. Master, New York, N.Y.
Donald W. McCauley, Okmulgee, Oklahoma
Donald R. McKay, Buffalo, New York
Frank A. Merlino, Providence, Rhode Island
Herman J. Moersch, Rochester, Minnesota
Edward H. Morgan, Seattle, Washington
J. Arthur Myers, Minneapolis, Minnesota
Rush E. Netterville, Jackson, Mississippi
Robert K. Oliver, Montgomery, Alabama
Richard H. Overholt, Boston, Massachusetts
Jerome V. Pace, Rockville, Indiana
J. Winthrop Peabody Sr., Washington, D.C.
Lloyd E. Peckenschneider, Halstead, Kansas
Charles K. Petter, Waukegan, Illinois
Charles Pokorny, Halstead, Kansas
Howell S. Randolph, Phoenix, Arizona
Elmer C. Rigby, Los Angeles, California
William R. Rumel, Salt Lake City, Utah
Paul C. Samson, Oakland, California
J. Gordon Seastrunk, Columbia, South Carolina
Joseph A. Smith, Glen Gardner, New Jersey
W. B. Steen, Tucson, Arizona
Lawrence H. Strug, New Orleans, Louisiana
James H. Stygall, Indianapolis, Indiana
Darrell H. Trumpe, Springfield, Illinois
Howard S. Van Ordstrand, Cleveland, Ohio
Raman Viswanathan, New Delhi, India
William C. Voorsanger, San Francisco, California
Dean C. Walker, Tulsa, Oklahoma
Buford H. Wardrip, San Jose, California
Irving Willner, Newark, New Jersey
W. Bernard Yegge, Denver, Colorado

Murray Kornfeld, Chicago, Illinois, Executive Director
Ward Bentley, Chicago, Illinois, Executive Assistant
Harriet L. Kruse, Chicago, Illinois, Executive Assistant
Margaret Rogers, Chicago, Illinois, Executive Assistant

The annual meeting of the Board of Regents was held on Wednesday, June 18, and the joint meeting of the Board of Governors and Board of Regents was held at a luncheon on Thursday, June 19. Dr. Seymour M. Farber, San Francisco, Vice President and Chairman of the Committee on General Arrangements for the meeting, was introduced and welcomed the College Officials to San Francisco. Dr. Farber and the members of his committees were congratulated on their splendid cooperation in the arrangements for the 24th Annual Meeting.

The following reports, resolutions and recommendations were approved by the Board of Regents.

Report of the Council on Postgraduate Medical Education

Our council is pleased to announce that five postgraduate courses on diseases of the chest have been presented under the sponsorship of the College during the past 12 months, all of them very well received and well attended. The 12th Annual Course was presented in Chicago, October, 1957, with a registration of 53 physicians; the 10th Annual Course in New York City, November, 1957, registration 119; the Third Annual Course in Los Angeles, December, 1957, registration 106; the 11th Annual Course in Philadelphia, March, 1958, registration 58 and one presented in Atlanta in March of 1958, registration 43.

This fall our program of postgraduate medical education will start with a special course on cardiopulmonary physiology to be presented as the 13th Annual Postgraduate Course of Chicago during the week of October 13-17. The 11th Annual Postgraduate Course on Diseases of the Chest will be presented in New York City, November 10 through 14, and the 4th Annual California Postgraduate Course on Diseases of the Chest will be presented in San Francisco February 16-20, 1959.

J. Winthrop Peabody Sr., *Chairman*

Report on College Books

The committee on books wishes to report that the following books sponsored by the American College of Chest Physicians have enjoyed remarkable sales. We have prepared this report to indicate the number of books printed, the number of books sold, and the number of each presently available.

ROENTGENOLOGY OF THE CHEST, Dr. Coleman B. Rabin, Chairman, Editorial Committee. Charles C Thomas Publishers, Springfield, Illinois. April, 1958. 3,000 printed—883 sold—2,117 available.

CLINICAL CARDIOPULMONARY PHYSIOLOGY, Dr. Burgess L. Gordon, Chairman, Editorial Committee. Grune & Stratton, New York City. February, 1957. 3,300 printed—3,300 sold—none available.

NONTUBERCULOUS DISEASES OF THE CHEST, Dr. Andrew L. Banyai, Chairman, Editorial Committee. Charles C Thomas Publishers, Springfield, Illinois. August, 1954. 3,152 printed—2,613 sold—539 available.

THE FUNDAMENTALS OF PULMONARY TUBERCULOSIS, Dr. Edward W. Hayes, Sr., Chairman, Editorial Committee. Charles C Thomas Publishers, Springfield, Illinois. February, 1949. 3,094 printed—2,695 sold—399 available.

It is gratifying to note that the book on *Clinical Cardiopulmonary Physiology*, which has been on the market only a short time, has been sold out and the committee is now engaged in a complete revision of this book which will be available early in 1959.

Upon the request of the publisher, the committee has also authorized a revision of the book on *Nontuberculous Diseases of the Chest*. Work on this new book has begun and it is hoped that the book will be available in 1959.

Another new book, *Diagnosis and Treatment of Tumors of the Chest*, which is being compiled under the chairmanship of Dr. David Spain of New York City, is well under way and we hope to be able to announce its publication early in 1959. The book will be published by Grune & Stratton.

Burgess L. Gordon, *Chairman*

Report of the Committee on Membership

Between September 1, 1957 and March 1, 1958, 305 applications from all parts of the world were received and presented to the Board of Regents. Of these applications, 160 were for Fellowship, 61 for Associate Fellowship, 44 for Associate Membership and 40 for advancement to Fellowship. Of this group, 196 applications were filed by physicians in the United States and Canada and 109 by physicians in other countries.

Of the total of 305 applications presented to the Board of Regents, 4 were rejected, 2 were tabled and 2 are being held for further investigation. Of the 82 physicians in the United States who applied for Fellowship, 14 have been reclassified as Associate Fellows.

With the admission of 257 new members in all parts of the world, the total membership of the College is now 6403. As of June 1, 1958, there were 72 applications pending presentation to the Board of Regents at the Interim Session. Other applications will, of course, be filed between now and September 1.

Chevalier L. Jackson, *Chairman*

Report of the Committee on Bronchoesophagology

The study of bronchography conducted by the Committee on Bronchoesophagology was presented at the Annual Meeting of the College in 1957 and was published in DISEASES OF THE CHEST in March, 1958.

The committee is presently engaged in the preparation of an editorial entitled "The Role of Endoscopic Photography in the Teaching of Bronchopulmonary Diseases." It is hoped that this editorial will be published in DISEASES OF THE CHEST and that reprints of this article may be sent to the deans of the various medical schools in order to acquaint these schools with the opportunities for visual aids in the teaching of bronchopulmonary disease.

At the Interim Meeting of the College in Philadelphia last December, our committee had an informal meeting at the Chevalier Jackson Clinic where we were guests of

Dr. Jackson and Dr. Norris. We had the privilege of witnessing quite a number of bronchoscopic and esophagoscopic examinations and had the opportunity to observe the technics used at the Jackson Clinic, as well as the new instruments. We hope to plan a similar informal type of committee meeting at the Interim Session in Rochester this fall.

Arthur M. Olsen, *Chairman*

BCG Statement

At a Congressional hearing in Washington, D.C., certain individuals stressed the use of public funds to support the wider use of BCG vaccination for tuberculosis in the United States. In view of the publicity given these hearings, the Executive Council of the College adopted the following statement which, it is hoped, will assist in clarifying the position of the College regarding the use of BCG in the campaign against tuberculosis in the United States.

In view of the vital interest in improving public health and welfare, and in the eradication of diseases of the chest in particular, our position regarding the use of BCG (bacillus Calmette-Guerin) against tuberculosis in the United States should be made known. At the present time there is insufficient evidence that significant protection is afforded by its use. The Council fully endorses the antituberculosis control program of the U.S. Public Health Service, which includes research in BCG, and urges the continued support of their program.

Resolutions

For a number of years, individual members of the College have presented subscriptions for the College journal, DISEASES OF THE CHEST, to their medical fraternities and sororities. These subscriptions have proved to be very popular with the members of the fraternities and sororities and it is recommended by the Board of Regents of the College that this program be expanded. A resolution was adopted by the Board of Regents recommending that College Chapters be encouraged to present subscriptions for DISEASES OF THE CHEST to the medical fraternities and sororities in their state or district. It is hoped that many of the College Chapters will endorse this worthwhile activity.

WHEREAS, The funds allocated for loan to accepted or acceptable candidates have earmarked approximately 30 per cent of the available funds set aside for resident loan purposes, and

WHEREAS, The nature of the fund shall ultimately become a revolving fund, and thereby it is hoped, be self perpetuating, but will not materialize in this manner until 5 or 6 years have elapsed and loan funds are repaid by the borrowers, together with interest at the rate of 3 per cent per annum, and

WHEREAS, The experience of the committee during the last year would indicate the desirability of accumulating a revolving fund of at least 25,000 dollars for loans to accepted candidates, and

WHEREAS, The anticipated budget of the College would be more satisfactorily adjusted to a small annual contribution rather than to one or more substantial contributions at intervals,

THEREFORE BE IT RESOLVED, That the College shall set up in its annual budget an amount of 2,000 dollars per annum for the resident loan fund until such fund shall reach the total sum of 25,000 dollars.

WHEREAS, Standards for Fellowship in the American College of Chest Physicians in the United States and Canada have been maintained at a high level by requiring that all candidates for Fellowship hold board certification or successfully complete our oral and written examinations, and

WHEREAS, These standards must be maintained at a high level throughout the world,

THEREFORE BE IT RESOLVED, That all candidates for Fellowship in the College in other countries be required to complete Fellowship examinations unless a waiver of this requirement is granted by the Board of Regents, or request of the Regent or Governor of that country and that such examinations shall be conducted under the supervision of the Regent or Governor of the country or territory concerned, or his appointee, and

BE IT FURTHER RESOLVED, That examinations for Fellowship be established at the earliest date in those countries in which this procedure has not already been adopted.

WHEREAS, The 25th Annual Meeting of the American College of Chest Physicians will be held in Atlantic City in June of 1959, and

WHEREAS, This Silver Anniversary Meeting will be given special and careful planning to make it the most outstanding meeting in the history of the College,

THEREFORE BE IT RESOLVED, That caps and gowns be worn at the 1959 Convocation of the College in order to lend additional dignity to this important function.

WHEREAS, The American College of Chest Physicians will celebrate its Silver Anniversary in 1959, and

WHEREAS, The first meeting of the College was held in Albuquerque, New Mexico, August 10th, 1935, and

WHEREAS, Invitations have been received from the Governor of New Mexico, the Mayor of Albuquerque, and the Presidents of the New Mexico State Medical Society and the Bernalillo County Medical Society to hold a Homecoming Meeting of the College in Albuquerque in 1959,

THEREFORE BE IT RESOLVED, That the American College of Chest Physicians hold its Silver Anniversary Homecoming Meeting in Albuquerque, New Mexico, October, 14-17, 1959.

It is recommended that a section on Nuclear Medicine be established to serve under the Committee on Physiologic Therapy of the American College of Chest Physicians.

The Board of Regents of the American College of Chest Physicians wishes to express its sincere appreciation to the following people for their efforts and cooperation in making the 24th Annual Meeting of the College a great success:

Dr. Seymour M. Farber and the members of the annual meeting committees.

Drs. Samuel Bellet and Peter Theodos and the members of their Committee on Scientific Program.

Dr. Paul H. Holinger and the members of the Committee on Motion Pictures.

Mrs. Seymour M. Farber and Mrs. Roger Wilson and the members of the Ladies Reception Committee.

The Staff of the Fairmont Hotel.

The San Francisco Convention and Visitors Bureau.

The press and radio station representatives of San Francisco.

Gold Medal Awarded by A.M.A.

Drs. Corrin H. Hodgson, J. A. Callahan, A. J. Bruwer and A. H. Bulbulian of the Mayo Clinic and Mayo Foundation, Rochester, Minnesota, were awarded the Billings Gold Medal for their exhibit on misleading thoracic roentgenograms in the Section on Diseases of the Chest of the American Medical Association meeting in San Francisco, June 23-27.

1958 Prize Essay Award Winners

Eugene A. Friedberg
University of Buffalo School of Medicine
First Prize

Ronald J. O'Reilly
University of California at Los Angeles, School of Medicine
Second Prize

Alan S. Deutsch
New York University School of Medicine
Third Prize

June Hagen
University of Cape Town Medical School
Honorable Mention

Report of the Committee on College Essay

The Committee on College Essay is pleased to report that 80 inquiries concerning the 1958 Prize Essay Contest were received from undergraduate medical students in the following countries: Argentina (2), Australia, Brazil, Canada (5), Chile, Czechoslovakia (2), England (7), France, India, Iraq, Ireland, Italy (2), Mexico, Nether-

lands, New Zealand, North Ireland, Pakistan, Philippines (2), Scotland, South Africa (2), Switzerland, United States (39), Uruguay, and Yugoslavia (2). Thirty applications for the contest were filed and 23 essays were submitted by students from the following schools:

Universidad Nacional, Argentina
Sydney University Medical School, Australia
University of Alberta, Canada
London Hospital Medical College, England
B. J. Medical College, India
Royal College of Medicine, Iraq
Queen's University, North Ireland
King Edward Medical College, Pakistan
Edinburgh University, Scotland
University of Cape Town, South Africa
University of Geneva, Switzerland

United States:
Jefferson Medical College (3)
State University of Iowa (2)
University of Minnesota
Georgetown University
State University of New York
University of Virginia
University of California at Los Angeles
University of Buffalo
New York University

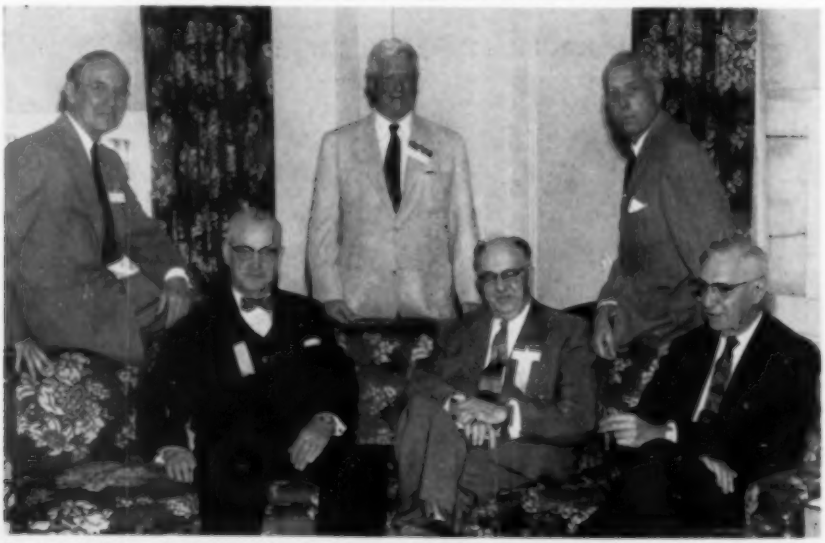
First Prize, consisting of $500, was awarded to Eugene A. Friedberg for his essay entitled "Murmur Production in Aortic Stenosis: An Analysis using a Hydraulic Model." Second Prize, $300, was awarded to Ronald J. O'Reilly for his essay on "Clinical Recognition of Carbon Dioxide Intoxication" and Third Prize, $200, was awarded Alan S. Deutsch for the essay "Ventricular Septal Defect: A Review." The committee awarded Honorable Mention and a prize of $50 to Miss June Hagen for her essay entitled "Cryptococcosis of the Lung."

1959 Essay Contest

The 1959 Prize Essay Contest is now open to undergraduate medical students throughout the world. Awards will be announced at the time of the 25th Annual Meeting of the College in Atlantic City, New Jersey, June 3-7, 1959, in the amounts of $500, $300, and $200 for first, second, and third prizes respectively. Each winner will also receive a certificate of merit.

The Board of Regents of the College requests the cooperation of members affiliated with medical schools in bringing the contest to the attention of the student body at their schools. Essays may be submitted on any phase of medicine or surgery relating to the diagnosis and/or treatment of cardiac or pulmonary diseases. The contest will close on April 15, 1959. Applications and instructions for the preparation of manuscripts may be obtained from the Executive Offices of the College, 112 East Chestnut Street, Chicago 11, Illinois.

Past Presidents of the College Meet in San Francisco



Seated, left to right: Dr. J. Winthrop Peabody, Washington, D.C.; Dr. J. Arthur Myers, Minneapolis, Minnesota; Dr. James H. Stygall, Indianapolis, Indiana; standing, left to right: Dr. Herman J. Moersch, Rochester, Minnesota; Dr. Burgess L. Gordon, Albuquerque, New Mexico, and Richard H. Overholt, Boston, Massachusetts.

College Councils and Committees Hold Annual Meetings in San Francisco

A typical committee meeting; Committee on Cardiovascular Diseases under the chairmanship of Dr. Arthur M. Master, New York City.

Fireside Conferences of 24th Annual Meeting

One of the Fireside Conferences held at the San Francisco meeting of the College on Friday, June 20.

Board of Governors and Board of Regents Meeting

The annual joint meeting of the Board of Governors and Board of Regents, Fairmont Hotel, San Francisco, Thursday, June 19, 1958.

Report of the Treasurer

STATEMENT OF INCOME AND EXPENSES FOR THE YEAR ENDED DECEMBER 31, 1957

INCOME:		
Annual Dues		$105,079.41
Fellowship Fees		24,496.50
Sales		
Advertising	$35,349.29	
Subscriptions	30,983.76	
Exhibit Space	2,477.71	
College Services—Net	13,662.50	
	$82,473.26	
Less—Discount Allowed	8,465.15	74,008.11
Interest Received on U.S. Bonds and Treasury Notes		1,317.45
Interest on Investment in Savings & Loan Associations		1,950.00
TOTAL INCOME		$206,851.47
EXPENSES:		
Salaries	$65,161.65	
Printing Journal	55,179.14	
Building Account (Schedule 1)	5,597.93	
Printing and Engraving	8,904.63	
Handling and Posting Journal	6,448.89	
Postage and Shipping	4,276.60	
Translations	300.00	
Officers' and Committee Expense	4,866.13	
Telephone and Telegraph	2,730.00	
Office Expense	2,584.44	
Traveling—Executive Director	1,596.95	
Annual Meeting	7,728.53	
Interim Meeting—Board of Regents	1,568.93	
International Meeting	8,464.99	
Public Relations Expense	1,757.69	
Editorial Board	4,018.75	
Hospital Counselor	1,028.90	
Library Expense	364.30	
Membership Certificates	456.52	
Payroll Taxes	1,026.65	
Prize Essay Award	1,174.74	
Audit	250.00	
Contribution to World Medical Association	500.00	
College Medals	43.95	
Contribution to National Society for Medical Research	25.00	
Depreciation—Furniture and Fixtures	1,668.40	
Total Expenses		187,723.71
NET INCOME		$ 19,127.76

Ralph H. Marcus, Certified Public Accountant, Chicago, Illinois

Charles K. Petter, *Treasurer*

College Chapter News

MICHIGAN CHAPTER

The Michigan Chapter will meet at the Sheraton-Cadillac Hotel, Detroit, on October 3. Dinner will be served at 6:30 p.m., to be followed by the scientific session at 8:00 p.m.:

"Clinical Application of Paper Electrophoreses in Sarcoidosis"
Nathan Levitt, Detroit

"Pulmonary Alveolar Proteinosis"
E. Osborne Coates, Jr., Detroit

KENTUCKY CHAPTER

The annual meeting of the Kentucky Chapter will be held at the Brown Hotel, Louisville, September 24. Guest speaker at the dinner meeting commencing at 6:30 p.m. will be Dr. Dwight C. McGoon, Rochester, Minnesota who will speak on "The Carcinoid Syndrome Associated with Malignant Bronchial Adenomas." In conjunction with the state medical association meeting, the chapter will present the following program at 2:00 p.m.:

"Lung Abscess"
Daniel Pickar, Louisville

"Pleural Biopsy"
Grover Sanders, Louisville

"Results of Non-operative Treatment of Bronchogenic Carcinoma"
John Paul Stamer, Louisville

"Surgical Treatment of Transposition of the Great Vessels"
Daniel Mahaffey, Houston, Texas

MEXICAN CHAPTER

The Mexican Chapter presented a Symposium on Chronic Cardiopulmonary Disease in conjunction with the National Institute of Cardiology in Mexico City, June 3-4. Prof. Dr. Ignacio Chavez, Director of the National Institute of Cardiology and an Honorary Fellow of the College, served as moderator. Over 600 physicians and medical students attended the symposium.

On August 5 the chapter presented the following program at a meeting held in Mexico City:

"Pulmonary Eosinophilia"
Raman Viswanathan, Delhi, India

"Surgery of Coarctation of the Aorta"
Fernando Quijano Pitman

The scientific session was followed by a buffet supper in honor of Dr. Viswanathan.

Lecturers at the Symposium on Chronic Cardiopulmonary Diseases and officers of the Mexican Chapter. Left to right, back row: Drs. Jorge Soni, Fernando Quijano Pitman, Ignacio Chavez, Aradio Lozano Rocha, Isaac Costero, and Pedro Guzzy. Center row: Drs. Donato G. Alarcon and Rosario Barroso. Front row: Drs. Victor Rubio, Miguel Jimenez, Rodolfo Limon-Larson, Ismael Cosio-Villegas, and Enrique Staines.

JAPAN CHAPTER

Members of the Japan Chapter who attended a special meeting in Tokyo, July 26, in honor of the visit to Dr. Seymour M. Farber, San Francisco, President-Elect of the College. Front row, left to right: Drs. Fumiyo Shimazu, Kingo Shinoi, Chuzo Nagaishi, Masao Tsuzuki, Masanaka Terada, Hiroshige Shiota, Seymour M. Farber, Taizo Kumagai, Yoneji Miyagawa, Jo Ono, Osamu Kitamoto, Harutaka Baba, Yoshio Hayashi, and Hirotake Tokugawa.

College News Notes

Dr. Andrew L. Banyai, Chicago, Illinois, was elected an honorary member of the Sociedad Colombiana de Tisiologia, Bogota, Colombia, and also of the Sociedad Antioquena de Tisiologia y Patologia Toracica, Medellin, Colombia.

The Iowa State Tuberculosis Sanatorium at Oakdale is celebrating its 50th anniversary this year. **Dr. William M. Spear** serves as Medical Director and Superintendent and other Fellows of the College on the staff are: **Drs. Philipp Cahn, Bernhard B. Gloeckler,** and **Daniel R. Webb.**

The honorary degree of Doctor of Laws was conferred upon **Major General Dan C. Ogle,** Air Force Surgeon General, on June 8 by his Alma Mater, Eureka College, Eureka, Illinois. General Ogle is Governor of the College for the Air Force. The degree, the highest honor given by Eureka College, was bestowed upon General Ogle in recognition of his exceptional achievements in his chosen career.

Dedication ceremonies for the Jacob J. Mendelsohn Laboratory at Fox River Hospital, Batavia, Illinois, were held on June 13. **Dr. Otto L. Bettag,** Chicago, Director of the Illinois Department of Public Welfare and Regent of the College, delivered an address at the dedication. **Dr. Mendelsohn,** a Fellow of the College for many years, passed away in 1955. He had served as medical director of the hospital for 29 years.

Major General Harry G. Armstrong, USAF (MC) was presented the Legion of Merit Award with Second Oak Leaf Cluster recently for exceptionally meritorious conduct in the performance of outstanding service to the United States as Surgeon of the United States Air Forces in Europe from July, 1954 to November, 1957.

Dr. Charles K. Petter, Waukegan, Illinois, was elected President of the Illinois Tuberculosis Association.

Dr. George L. Waldbott, Detroit, Michigan, received first prize for an exhibit on Contact Dermatitis at the Session on Occupational Allergy of the European Academy of Allergy in The Hague, Netherlands recently.

Major Khushdeva Singh, Superintendent of the Tuberculosis Centre, Patiala, India, and for many years Secretary of the North India Chapter of the College, was awarded the honor of "Padam Shri" by the Government of India for his

outstanding work in the field of tuberculosis and diseases of the chest. The honor was conferred by the President of the Government of India at Government House in New Delhi.

Dr. Francis J. Weber, Washington, D.C., has been appointed Chief of the newly established Division of Radiological Health of the Public Health Service.

Dr. Jethro Gough, Cardiff, Wales, recently lectured at the Mayo Clinic and Mayo Foundation, Rochester, Minnesota on the subject "Some Recent Investigations in Pulmonary Pathology."

Dr. Harry Golembe, Liberty, New York, has been elected Vice-President of the Medical Society of the State of New York.

Colonel Weldon J. Walker was a guest speaker at the Eighth Middle East Medical Assembly held May 9-11 at the American University in Beirut, Lebanon. Colonel Walker presented papers entitled "Newer Concepts Concerning the Cause and Prevention of Hypertension" and "The Lipid Problem in Atherosclerosis."

Announcements

We are pleased to report that the book, CLINICAL CARDIOPULMONARY PHYSIOLOGY, edited by Dr. Burgess L. Gordon and sponsored by the American College of Chest Physicians, has enjoyed such a large sale that stock on this book is now entirely depleted. It is requested that orders for this book be withheld until the announcement of a new revised edition which is now being prepared by the College. Release of this revised edition is anticipated early in 1959.

The next Postgraduate Course in Laryngology and Bronchoesophagology to be presented by the University of Illinois College of Medicine is scheduled for October 27-November 8, 1958. The course is under the direction of Dr. Paul H. Holinger. Interested registrants may write directly to the Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

A three-day postgraduate course on cardiopulmonary diseases will be held in Denver, Colorado, October 16-18, 1958, under the sponsorship of the Colorado Chapter of the American College of Chest Physicians, Colorado Heart Study Group, Fitzsimons Army Hospital, National Jewish Hospital, and the University of Colorado School of Medicine. Outstanding speakers will lecture at this postgraduate course. For further information, please communicate with the Office of Postgraduate Medical Education, University of Colorado Medical Center, 4200 East Ninth Street, Denver, Colorado.

Special Postgraduate Course

CLINICAL CARDIOPULMONARY PHYSIOLOGY

Edgewater Beach Hotel, Chicago, Illinois

October 13-17, 1958

Have you received your copy of the program for this special postgraduate course? If you are interested in attending this course, please write to the Executive Offices of the American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois, for a copy of the program.

Enrollment is limited.

Applications will be accepted in the order received.

MEDICAL SERVICE BUREAU

Position Wanted

Residency-trained chest clinician seeks directorship of small chest hospital or chest service unit of hospital. Background includes 10 years full-time department head of chest and bronchoscopic services of large county institution. Broad administrative experience; F.C.C.P., F.A.C.S. Please address inquiries to Box 301B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Positions Available

Full-time chest physicians wanted for positions in state mental hospitals in midwestern state. Assignments include diagnosis, therapy and research. Salaries range from $7200 to $20,000 per year, depending upon position, education and experience. Nominal deduction for maintenance. Civil Service, liberal pension plan, sick leave, annual paid vacation. Requirement: graduation from an approved medical school and one year rotating internship. Training in chest diseases. Please address all inquiries to Box 298A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Physician wanted for approved residency in tuberculosis. Accredited bicounty hospital, 219 beds pulmonary diseases, 30 beds rehabilitation chronic illness. Starting salary $600 monthly, includes furnished modern house for family. Must be eligible for California license. Write: Medical Director, Tulare-Kings Counties Hospital, Springville, California.

Staff or resident physician wanted for 130-bed accredited tuberculosis hospital. Must have or obtain Indiana license. Salary $500 per month or more, depending upon qualifications. Family maintenance, three bedrooms, two baths, garage, food, laundry. Social Security, pension plan. Apply: Director, Healthwin Hospital, South Bend, Indiana.

CALENDAR OF EVENTS

NATIONAL MEETING

Interim Session
American College of Chest Physicians
Rochester, Minnesota, November 29-30, 1958

Semi-annual Meeting, Board of Regents
American College of Chest Physicians
Minneapolis, Minnesota, December 1, 1958

POSTGRADUATE COURSES

13th Annual Course, "Clinical Cardiopulmonary Physiology"
Chicago, Illinois, October 13-17, 1958

11th Annual Course on Diseases of the Chest
New York City, November 10-14, 1958

CHAPTER MEETINGS

Kentucky Chapter, Louisville, September 24

Colorado Chapter, Colorado Springs, September 28

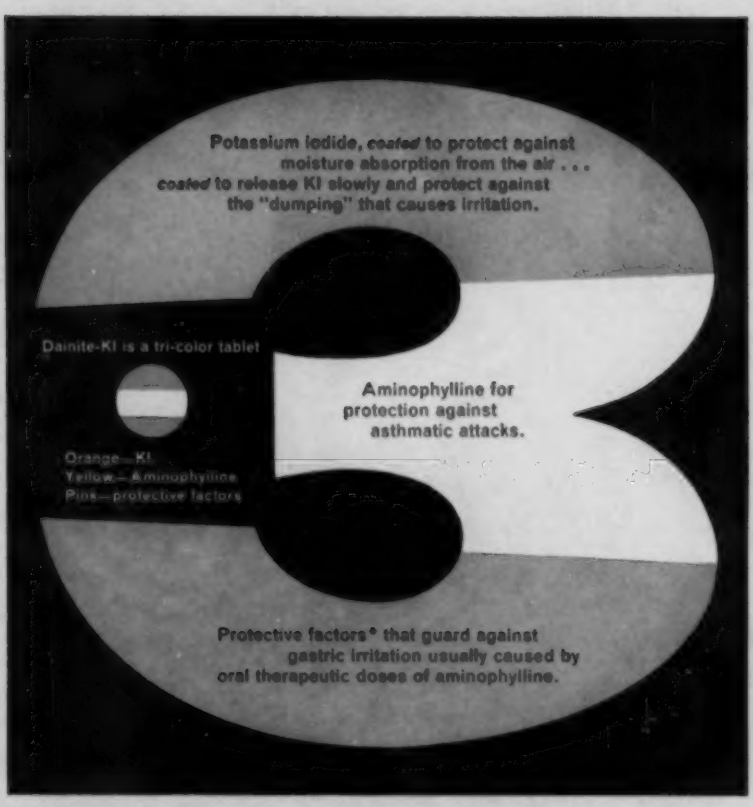
Michigan Chapter, Detroit, October 3

Virginia Chapter, Richmond, October 12

Southern Chapter, New Orleans, November 2-3

Pacific Northwest Chapter, Vancouver, B.C., November 7-8

Potomac Chapter, Washington, D.C., November 23



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✓ Provides extra bronchodilatation	Ephedrine HCl	¼ gr.
✓ Calms the patient	Phenobarbital	⅛ gr.
✓ Protects against gastric irritability	Ethyl aminobenzoate	¼ gr.
	Aluminum hydroxide	2½ gr.

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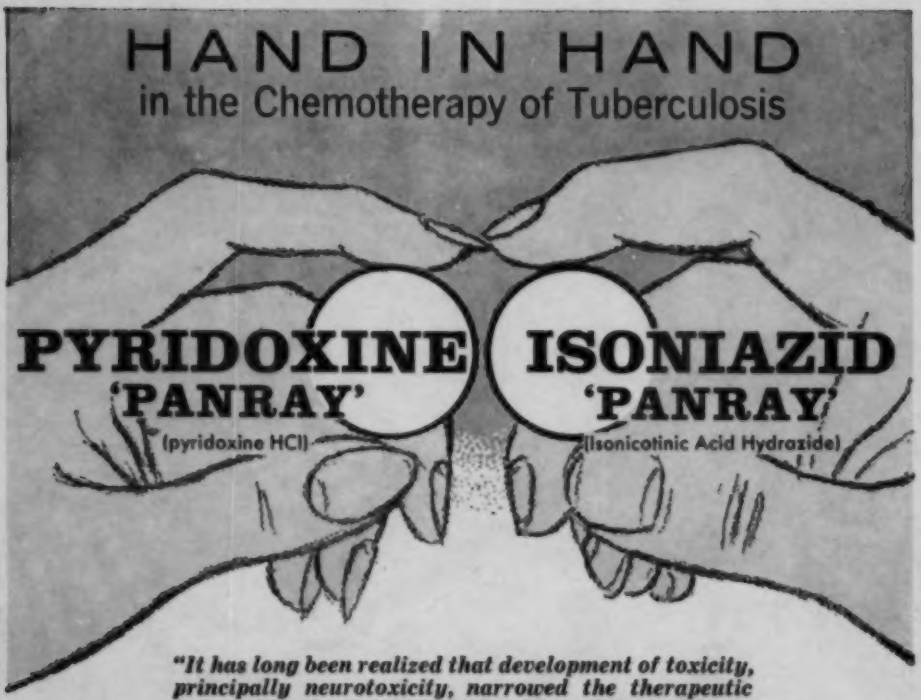

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[1]Sea View Bulletin 16:62 July '56 Tchertkoff, et al. JAMA 156:1549 (Dec. 25) 1954 Biehl & Viltner Am. Rev. Tbc 70:266 Aug. '54 Hughes, et al. N. Eng. J. of Med. 255 #3 118-122, 1956 Carlson, et al.